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AN ANALYSIS OF DUODENAL ULCER THERAPY

Thesis for degree of MD

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This thesis is based primarily on studies carried out under the supervision of Dr K G Wormsley, Consultant Gastroenterologist and Reader in Clinical Pharmacology at Ninewells Hospital and Medical School, Dundee. Although part of a research team which included Dr E J S Boyd, Dr J Penston and Dr D Johnson, I carried out the majority of the work for each of the projects with the exception of the section on duodenal ulcer maintenance with ranitidine. Although I contributed, both in the endoscopy and clinic sessions, to the review of these patients, Dr Boyd was first author but has kindly given me permission to quote this work. The study on the healing of duodenal ulcers with ranitidine was carried out during my military service as a three-centre trial. I was responsible for one centre in Germany, under the supervision of Maj Gen (then Col) D M Roberts. The duodenal ulcer healing study with omperazole was carried out as a multi-centre trial, headed by Dr JH Baron. I was responsible for data collection for our centre, and represented the centre during the drafting of the paper for publication. The section on the use of omeprazole for refractory ulcer was also based upon a three-centre trial - two centres in Holland and one centre, for which I was responsible, in Dundee and the project was supervised by Prof GNJ Tytgat. The section on mucosal prostaglandin content and the review of pirenzepine in the therapy of duodenal ulcer was undertaken with Prof R H Hunt, Department of Gastroenterology, McMaster University, Canada, while working there as a Research Fellow. Publications and presentations arising from these studies are listed overleaf.

PUBLICATIONS AND PRESENTATIONS ARISING FROM STUDIES

1. Wilson JA, Hunt RH, Derodra JK et al. Antacids for duodenal ulcer - how low can we go? Submitted to BSG Sep 1986

2. Wilson JA, Hunt RH, Derodra JK. Prostaglandin content of rat gastric mucosa - effect of size of biopsy forceps. Submitted to BSG Sep 1986.

3. Penston J, Wilson JA, Johnston D, Wormsley KG. Inhibition of nocturnal gastric secretion by trimoprostil, a synthetic prostanoid. Curr Med Res Opin 1986;10(3):145-149

4. Wilson JA, Johnston D, Wormsley KG. Effect of enprostil on nocturnal gastric secretion in volunteers. Presented to Cal Soc Spring 1985

5. Wilson JA, Read J, Boyd EJS et al. Effect of trimipramine on pentagastrin-stimulated and overnight secretion. Presented to Scottish Soc Exp Med Autumn 1982

6. Wilson JA, Read J, Boyd EJS et al. Inhibition of pentagastrin-stimulated and overnight gastric secretion by mianserin. B J Clin Pharm 1983;15:329-333

7. Wilson JA, Boyd EJS, Wormsley KG. Effects of some polycyclic drugs on gastric secretion and the healing of duodenal ulcers. Act Psych Scand 1985;72:93-97

8. Wilson JA, Hunt RH. The role of pirenzepine in the short- and long-term therapy of duodenal ulcer. In: Pirenzepine - knowledge and new trends. (Eds) Cheli R and Molinari F. Raven Press, New York, 1986 pp 21-28

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10. Wilson JA, Johnston D, Penston J, Wormsley KG. Inhibition of human gastric secretion by ICI 162,846, a new histamine H2 receptor antagonist. Br J Clin Pharm 1986; in press

11. Roberts DM, Wilson JA, Ratcliffe G et al. Clinical trial of ranitidine in the treatment of peptic ulcer in service personnel. B J Clin Prac 1982;36:9-12

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13. Wilson JA, Boyd EJS, Wormsley KG. Effect of intraduodenal omeprazole on gastric acid and pepsin secretion. Presented to American Gastroenterology Association Spring 1983

14. Wilson JA, Boyd EJS, Wormsley KG. Omeprazole inhibits nocturnal and pentagastrin-stimulated gastric secretion in man. Dig Dis Sci 1984;29(9):797-801

15. Pounder RE, Misiewicz JJ, Wilson JA et al. Omeprazole for duodenal ulceration: tolerance, acid inhibition, endoscopic healing and recurrence. Br Med J 1984;289:525-528

16. Tytgat GN, Lamers CB, Wilson JA et al. 100% healing with omeprazole of peptic ulcers resistant to histamine H2 receptor antagonists. Gastroenterol 1986;88:1620

17. Wilson JA, Boyd EJS, Wormsley KG. Safety profile of omeprazole - a new ulcer healing drug. Presented to 12th Int Cong Gastroenterol Sep 1984

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1 INTRODUCTION

1.1 Epidemiology

Duodenal ulcer, for the purposes of these studies, is defined as a breach in the duodenal mucosa, which extends through the muscularis mucosa (189). Estimating the incidence of duodenal ulceration within a given population is fraught with difficulty: ulcers may be asymptomatic (56); the patient may tolerate the symptoms or treat him/herself with over-the-counter medication; the general practitioner may treat without investigation to confirm the diagnosis; or the patient may be either inadequately documented or inadequately investigated on referral to a hospital specialist.

1.1.1 Disease Markers

The criteria for estimation of ulcer disease within the population has also varied considerably - the incidence of surgical procedures for ulcer; the rate of hospital admissions and discharges for perforation; the death rate from peptic ulcer; and evidence of ulceration at autopsy have all been utilised (231,418,120,339,404,190). Geographical varia tions in annual incidence makes comparison, not only between countries but also between regions, difficult to interpret. In the UK, for example, duodenal ulcer incidence decreases from North to South (228) but in Norway (287) and India (228), as one travels in a northerly direction, ulcer incidence decreases.

In Europe one of the most exhaustive and prospective studies has been based on findings at autopsy in Leeds (404), with estimates of the incidence of duodenal ulceration in males over the age of 35 years of one in ten. This estimate is of the same order as in the necropsy

analysis by Ivy from the United States in the same period (190). In women, however, ulcers were found in only one person in sixteen.

1.1.2 Time-trends

As duodenal ulceration is a chronic disease, cross-sectional studies of the same region at different time periods will almost certainly include many of the same individuals on many occasions. If the rate of death of patients with duodenal ulcer disease were unchanged over the decades, any alteration in the total population with ulcers would be a true reflection of changes in the number of patients acquiring the disease. Although that assumption is not true, estimates can be made both from changes in the total population number and from changes in the death rate. One is still left, however, with the problem that the disease may last a variable length of time, the average of which in a population may change from decade to decade. The proportion of "new" cases in any cross-sectional study may therefore be different from one decade to the next Changes in the occurrence of the disease during a period of time are best assessed from studies based on new cases, both in hospital and general practice. The earliest study of this type was published by Doll in 1951 (97).

Hansen (156) noted a six fold increase in the number of patients hospitalised in Copenhagen during the first thirty five years of this century. Fig 1.1 I is adapted from an excellent review article by Bonnevie (287) and depicts a three fold rise in the incidence of perforated ulcers in Scotland during the 25 years from 1924 but, when the figures for 1970 and 1975 are viewed in the context of the preceding two decades, it seems likely that the value for 1968 is spuriously high

and there has, in fact, been little change from 1950. These data are generated from several separate studies (183,193,245,341).

If time-trends are to be meaningfully examined then prospective or repeated cross-sectional studies of a geographically well-defined population are required. Only a few studies accommodate these criteria. In York, there was a decrease in the rate of duodenal ulcer in males from 1952 to 1963 (314,315) while in Copenhagen, during the subsequent six year period, no significant change was observed (44,45,48). Jonasson demonstrated that the incidence of new duodenal ulcer cases in Iceland remained virtually unchanged between 1970 (2.1/1,000) and 1980 (2.0/1,000), although the rate was increasing in females and decreasing in males (199).

In the United States, both Fineberg (120) and Smith (352) have assessed the decline in ulcer surgery. Fineberg went on to assess the incidence of surgery in the two years following the introduction of cimetidine and concluded that the decline to a level less than that predicted was due to the effect of the drug. Mendeloff (264), in his review, felt that the available data did not permit definite conclusions and made a plea for improvement in clinical records.

Throughout the rest of the world, values are also available from Israel (421), Australia (177), including an analysis of data referring to aborigines (24), Japan (362), India and Ethiopia (248,380). Local geographic variations in prevalence, with a weighting towards urban communities, and a gradual fall in incidence over the last 30 - 40 years are all points which emerged also from the European and North American studies.

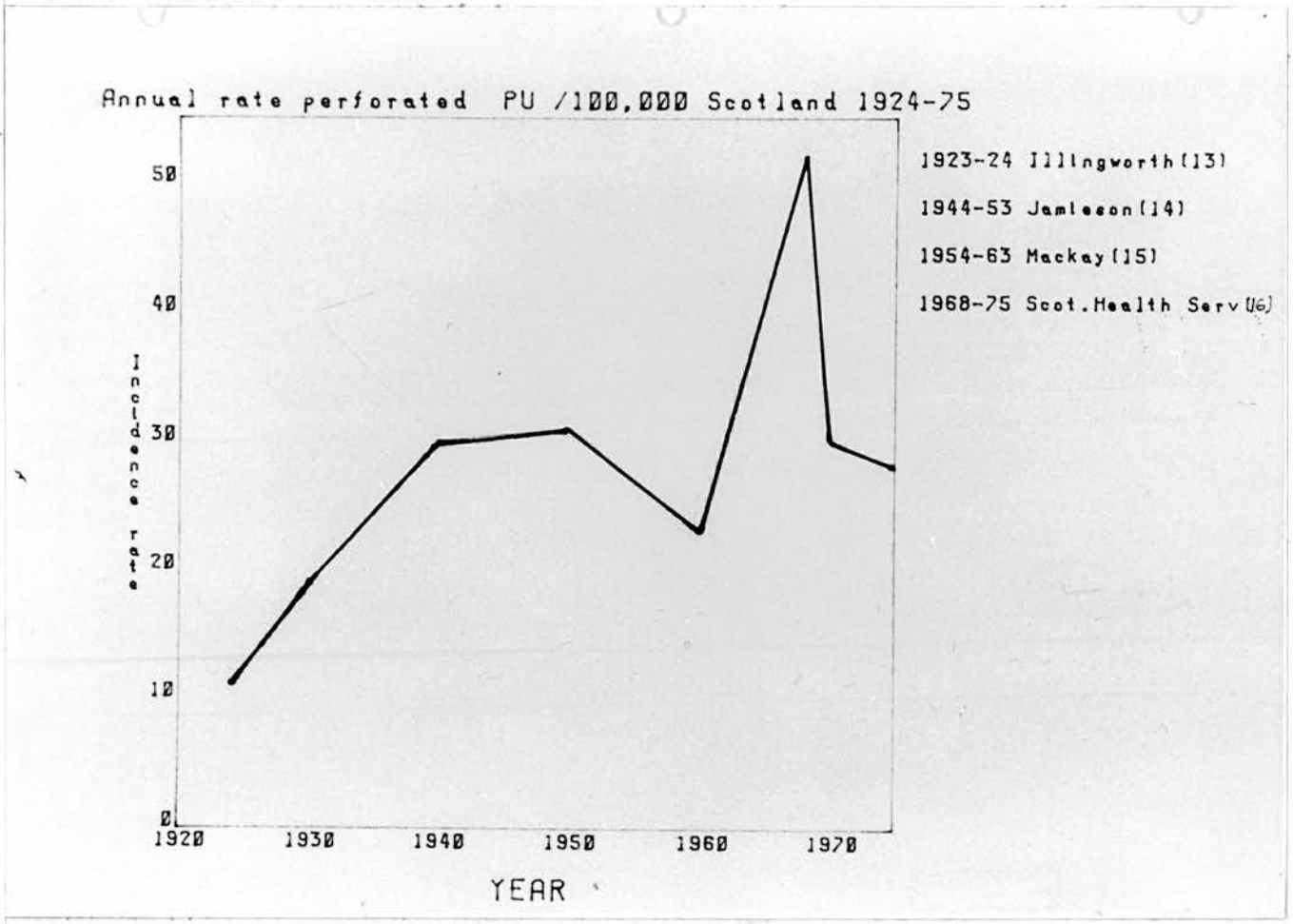
1.1.3 Urban vs Rural

In an attempt to interpret the world literature on ulcer epidemiology, Susser (371) has stated in his review that duodenal ulceration is a disease of "early urbanisation" - as the disease declines in the predominantly white populations of Western Europe and North America he predicts an increase in previously disadvantaged Third World populations as they move into the cities. This concept is supported by data from South Africa (342) and Zimbabwe (123), in that the diagnosis of duodenal ulcer is being made increasingly frequently in black Africans who have settled in Salisbury and Harare. This also holds true in an Australian study (24) which retrospectively found that in the period before significant urbanisation, there was a striking absence of duodenal ulcers in the aborigine population.

1.1.4 Summary

In many parts of the world the incidence of new cases of duodenal ulceration has been falling during the last four decades, long before the introduction of modern anti-ulcer therapy. On the other hand, studies of time trends in other defined populations show that the incidence and prevalence rates have not changed, or have increased, with clear implications both for our understanding of ulcer aetiology and for the planning future health resources.

Fig 1.1 I Annual rate perforated peptic ulcer in Scotland 1924-1975



1.2 Pathogenesis

1.2.1 Introduction

The "Sword and the Shield" is a concept which has been proposed by Hunt (181) in discussing both ulcer aetiology and therapy, and is used in this review as a frame of reference when considering aggressive and defensive factors in the preservation of mucosal integrity. Despite the many facets of ulcer disease of which we remain ignorant, such as why ulcers are focal; why they remit and relapse; and why only some are painful, it seems that peptic ulcers are still appropriately named because they depend on the presence of gastric juice. Thus, in patients with pernicious anaemia who cannot secrete acid or pepsin, ulcers are extremely rare. In contrast, less than 10% of patients with the hypersecretory state of Zollinger-Ellison syndrome do not develop ulcers.

1.2.2 Histamine

There are three major classes of chemical messengers - endocrine, paracrine and neurocrine - which regulate function within the body, and all three are important in the regulation of acid secretion (114,146). This is illustrated in Fig 1.2 I which is adapted from Soll (356). These three mechanisms together form a group of potential pathways for the inhibition of gastric secretion:

1. Inhibitors of cell receptors	Histamine H2 receptors
	Muscarinic receptors
	Gastrin receptors

In addition, gastric parietal cells can be inhibited by blocking intracellular processes involved in acid secretion:

2. Inhibitors of cell activation	Prostaglandins E and I

3. Inhibitors of proton pump Substituted benzimidazoles

Two hypotheses have been proposed for the involvement of histamine in the stimulation of gastric secretion. Firstly, it has been suggested that histamine, released as paracrine agent, acts as a "final common pathway" for stimuli acting not only to release histamine directly but also stimuli acting on cholinergic and gastrin receptors. The latter were considered somehow to release histamine which, in turn, activated the histamine receptors of the parietal cell (73). Alternatively, it was proposed that each parietal cell had receptors for histamine, acetyl choline and gastrin and that these receptors were functionally interdependent, so that blockade of one interfered with the efficacy of the stimulus to the parietal cells provided by the other two (144).

The possibility that histamine was the final common pathway for paracrine stimulation of the parietal cell was hotly debated for many years (74,198,75,360), but the observation that H2 antagonists blocked not only the stimulatory effects of histamine, but also of gastrin and vagal stimuli, seemed to provide strong evidence that histamine played an important role in the regulation of all these major pathways (40,135,144).

Histamine is formed by decarboxylation of L-histidine through the action of the enzyme histidine decarboxylase (HDC). Although a second (DOPA) decarboxylase exists in mammalian gastric mucosa, this does not seem to be involved in significant histamine formation in vitro (12). Histamine degradation is primarily by methylation, through the action of histamine methyl transferase (HMT) although oxidative deamination of the side chain also occurs through the action of a group of enzymes called the diamine oxidases.

In man, the concentration of histamine is greatest in the corpus, intermediate in the fundus and least in the gastric antrum. At the cellular level, the distribution of histamine in the rat is highly correlated with HDC and the cellular fractions with the highest content of these substances contains 8-12% of a cell population whose electron microscopic appearances are those of enterochromaffin-like (ECL) cells. It is estimated that the concentration of histamine within the ECL cells is about 2-8 pg/cell, which is lower than the 17 pg/cell for the mast cell population (357) but of a similar order to dog mucosal mast cells (354). Lorenz has been careful to distinguish, both in human and canine gastric mucosa, between the atypical and the typical mast cells, since the former contain 90% of the histamine content of the mucosa. He concluded that in humans, atypical mast cells within the gastric mucosa are histamine stores which release histamine and so stimulate the parietal cell (379). The existence of specific binding sites on the parietal cell for different gastric stimulants is still in doubt though Soll (359) has demonstrated binding of gastrin 17 to canine parietal cells.

Lorenz and co-workers have shown that the gastric mucosal histamine content of duodenal ulcer patients is less than the levels in controls subjects (381,382,244,379) and this finding has been confirmed by other workers (249). Although the evidence in animals is conflicting (330,318) studies in human volunteers (242) and duodenal ulcer patients (250) have shown an increase in the output of histamine during pentagastrin stimulation. Not only has an inverse relationship been demonstrated between individual peak acid outputs and mucosal histamine concentrations but a direct relationship has also been demonstrated between the decrease in peak acid output after vagotomy and the rise in

mucosal histamine (243).

One of the questions which remains unanswered is whether the differences in mucosal histamine content in patients with duodenal ulcer is a result of acid hypersecretion or whether mucosal histamine occupies a primary place in altering secretory status and thus contributes to the pathogenesis of ulcer disease. This topic has been recently reviewed by Parsons (291). The role of histamine in the control of gastric secretion, and the effect on histamine metabolism of H2 receptor antagonists, is further considered in Ch 6.1.

1.2.3. Acid

The average rate of acid secretion in duodenal ulcer patients is higher than that in controls, although about two thirds of patients secrete within the normal range. While patients with gastric ulcer tend to have decreased acid secretion, most of them secrete within the normal range. Figure 1.2 II depicts the trends and overlaps in the various secretory states and is adapted from the monograph by Dr J H Baron (23). Peptic ulcer results from an imbalance between the acid and pepsin to which the duodenal mucosa is exposed and the capacity of the mucosa to resist the damage resulting from that exposure. In addition to noting the overlap between maximal acid output of normal individuals and duodenal ulcer patients, Sircus divided ulcer patients into three groups according to basal and stimulated acid outputs - a) both elevated b) both normal and c) elevated basal but normal stimulated (350). The possibility that the higher acid output might be secondary to the formation of an ulcer has been considered (119) but the evidence from South Africa to support this has been severely criticised on statistical

grounds (351). There is now some evidence (176) that the concentration of acid delivered to the duodenum is more important than the total acid load (the product of concentration and volume) in ulcerogenesis. Certainly, the regimens of H2 receptor antagonists in current use suppress concentration to a greater degree than the anticholinergic drugs which have been used to heal ulcers, and this is consistent with the higher healing rates obtained with H2 receptor antagonists .

Clarification of the relative importance of acid concentration and acid load in ulcer healing may also help to clarify the role of acid in ulcer pathogenesis. Studies which address this issue, however, face a number of methodological problems in assessing gastric acid secretion, particularly during 24hr studies. Thus, if one approximates the physiological situation by normal feeding, total 24 hr aspiration is impossible but measuring hydrogen ion concentration or pH in aliquots of gastric contents throughout the day does not permit assessment of acid output, which is, in part, dependent on the rate of gastric secretion (volume of gastric juice). A recent paper from the Dallas group (116) has partially overcome this problem by performing aspiration during nocturnal and interprandial periods, and intragastric titration during postprandial periods. In this study, 24hr acid output was almost twice as high in 8 duodenal ulcer patients as in 7 normals indivduals. Although cimetidine 400mg twice daily reduced acid output in the ulcer group to levels not significantly different from controls before treatment, parietal cell vagotomy reduced acid output by a further 50%. The authors concluded that the findings of their study support the concept that both diurnal and nocturnal acid secretion are important in ulcer pathogenesis, quoting studies (296,186) which rely mainly on diurnal or nocturnal secretory control yet which both effectively accelerate

ulcer healing. On the other hand, Jones et al (176) have demonstrated a highly positive correlation between the level of suppression of nocturnal acid concentration and the healing rates obtained with any particular drug. It may be that, as the Dallas group have demonstrated, acid secretion in ulcer patients is increased throughout the 24 hours but that nocturnal secretion, when acid is not buffered by food, is more important in ulcerogenesis. Boyd (53) has, however, noted that there was no discernible relationship between nocturnal acid suppression and ulcer healing, although the number of patients in the study was too small to permit a statistically powerful conclusion.

That acid is important in duodenal ulcer disease is evident from the efficacy of the H2 receptor antagonists in healing ulcers. In the next two sections the roles of histamine and gastrin in the control of acid secretion and the pathogenesis of duodenal ulcer disease will be considered.

1.2.4 Gastrin

Although Edkins (103) was the first to observe that intravenous injections of extracts of antral mucosa stimulated acid secretion in animals, naming the active factor gastrin, much criticism and controversy surrounded this work because the extracts also contained histamine. Some thirty years later it was shown that histamine free extracts still caused stimulation of acid secretion (212) but the controversy continued. It was only with the isolation of pure gastrin from hog antral mucosa (143) that this controversy finally ended. Since

the successful immuno-assay of gastrin by McGuigan in 1968 (258), the role of this hormone in gastric secretion and in the pathogenesis of ulcers has been extensively reviewed (397,398,259).

Although the presence of marked hypergastrinaemia due to the Zollinger-Ellison syndrome causes duodenal ulceration in more than 90% of patients, duodenal ulcer patients have been reported both to show increased basal and/or postprandial gastrin levels (224,113,77) or to have values not significantly different from control (non-ulcer) subjects (259). There remains, however, the possibility of increased gastric sensitivity to the effects of gastrin, as demonstrated by pentagastrin infusion in patients with duodenal ulcer (224).

1.2.5 Pepsin

The role of pepsin in the pathogenesis of duodenal ulcers remains an enigma. There is clear evidence (337) that experimental ulceration of stomach, duodenum and jejunum is not possible with acid alone, but requires the presence of pepsin. Increased pepsin secretion in ulcer disease has been noted (390,376), although an earlier study (179) found that pepsin secretion was of the same order as in normals. H2 receptor antagonists have been reported to increase (65,139), leave unchanged (335) and decrease (241) pepsin secretion. Two reasons for the discordance in these findings are the variability of biological assays and the fact that, as peptic activity is pH dependent, changes in gastric pH effected by H2 receptor blockade will cause changes in peptic activity (34).

Two sub-types of the precursor of pepsin, pepsinogens I and II can be measured in serum. Although this may be of interest on an epidemiological basis - serum pepsinogen I and II are both elevated in

duodenal ulcer, an elevated serum pepsinogen I was associated with a threefold higher odds ratio for duodenal than for gastric ulcer and an elevated serum pepsinogen II was associated with a three fold higher odds ratio for gastric than for duodenal ulcer (333) - the relationship between serum pepsinogen and gastric pepsin secretion has not been established.

1.2.6 Campylobacter Pyloridis

Although the majority of the research which has been undertaken on aggressive factors in ulcer pathogenesis has been concerned with the role of acid and pepsin, the concept that bacteria might play a part in breaching the mucosal barrier has been suggested in recent years as a result of the finding and study of a campylobacter-like organism (CLO or C. pyloridis. "Spirochaete organisms" were first reported in the stomach of the dog almost one hundred years ago (39), and, fifty years later (79,96) in both monkey and human stomach. After Warren's initial report in 1983 (403) several groups around the world have examined gastric mucosal biopsies by culture and microscopy for these organisms (251,328,201,262,252,227,64,267,309,178,301,253,254). To date, no convincing evidence has been produced that the organism causes ulceration, although there does seem to be an association with antral gastritis.

1.2.7 Herpes simplex

There is a striking similarity between the clinical course of duodenal ulceration and of aphthous ulceration of the buccal mucosa. The aetiology of pain in both conditions, which remit and relapse without

demonstrable cause, is poorly understood. Although infection with herpes simplex causes small vesicles which disappear spontaneously and peptic ulcer runs a protracted course, often with deep ulceration, Borg (49) has suggested that these differences may be accounted for by the effect of acid and pepsin in the duodenal bulb. A study of patients undergoing vagotomy for peptic ulceration reported that 90% were carriers of herpes simplex (3). Antibodies to this virus have been found both in serum (391) and in duodenal fluid (329) in a significantly greater proportion of patients with active duodenal ulcer than in normal controls.

1.2.8 Prostaglandins

Prostaglandins are ubiquitous hormone-like substances, unstable with biologically active metabolites, and present in minute amounts in almost all body tissues. They have been shown to fulfill three roles in maintaining the integrity of the mucosa of the upper alimentary tract: 1) Inhibition of gastric secretion 2)"Cytoprotection" - prevention of damage to the sub-epithelial layers of mucosa from agents such as ethanol and aspirin 3) facilitation of mucosal repair. Malagelada's group from the Mayo Clinic (2) have demonstrated that prostaglandin synthesis in the duodenal mucosa is increased in response to a meal in normals, but not in duodenal ulcer patients. In addition, in animal studies, it has been shown that perforated ulcers, just distal to the pyloroduodenal junction developed in 7 of 10 rabbits used for production of high titre plasma antibody to 6-keto PGF1 alpha and PGE2. The remaining rabbits developed imperforated ulcers or gross erosions (285). Interpreting these findings as indicating that prostaglandins have a protective effect on the gastric and duodenal mucosa may be an oversimplification, however, as PGE2 inhibits gastric acid secretion

(26) and indomethacin, a prostaglandin synthesis inhibitor, stimulates acid production (115). Reference has already been made (Ch 1.2.3) to the study relating the efficacy of ulcer healing compounds to their antisecretory effects (176). The ability to heal ulcers of some of the synthetic prostaglandins is exactly as one might predict from their inhibitory effect. The ulcer healing ability of these compounds may therefore be related more to acid inhibition than cytoprotection, a concept which is explored further in Ch 4.

1.2.9 Gastric Mucosal Bloodflow

Focal reductions in gastric mucosal bloodflow, with resultant ischaemia, have been proposed as a possible explanation for the restricted area of mucosa involved in gastric and duodenal ulcer disease (145). The methodology to confirm this hypothesis is currently inadequate. Clearance techniques (191) and the use of radioactive microspheres (11) do not permit rapid repitition of measurement or assessment of focal areas of relative ischaemia, although the latter technique has been used to show that increases in gastric mucosal bloodflow during sepsis in an animal model may be prostaglandin-mediated (282) and that the mucosal ischaemia associated with stress-ulcers may be reversed by topical PGE2 (129).

Cysteamine, a known ulcerogen, has been reported to cause an increase in rat gastric mucosal bloodflow when measured by microsphere (372) but a decrease in the same parameter is detected when measured by hydrogen clearance (420). Szabo, in his review (373), concludes that although decreased bloodflow is probably not sufficient to initiate localised duodenal ulceration, exposure of ischaemic mucosa to

unbuffered acid in the duodenal bulb may induce such lesions.

1.2.10 Mucus and Bicarbonate

Nearly thirty years ago Heatley (163) proposed the concept of a pH gradient across the gastric mucus barrier. This role of mucus and bicarbonate secretion as factors in the protection of the gastric mucosa was reviewed by Allen and Garner (4), who drew particular attention to the depth of the gel layer, the ability of luminal acid to stimulate the secretion of bicarbonate and the special resistance of certain cell membranes, such as those of the gastric glands, which are not covered by mucus. Prof Allen has also contributed to a study suggesting that the peptic activity of gastric juice from duodenal ulcer patients is mucolytic at higher pH than is the juice from non-ulcer control patients (182). Associated with this is the finding that the thickness of the mucus layer is significantly less in patients with duodenal ulcer (81).

Fig 1.2 I Endocrine, paracrine and neurocrine control of parietal cell

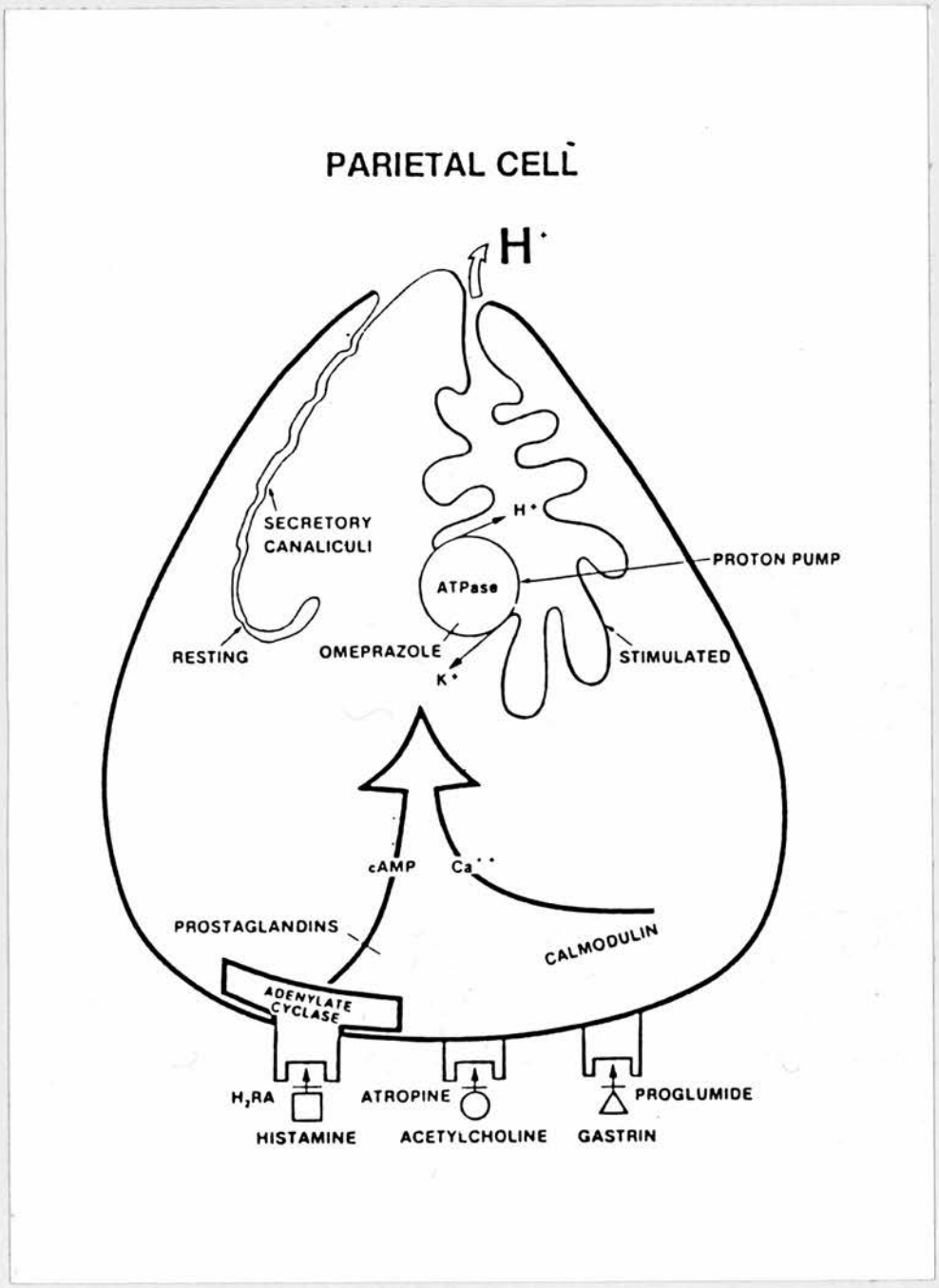
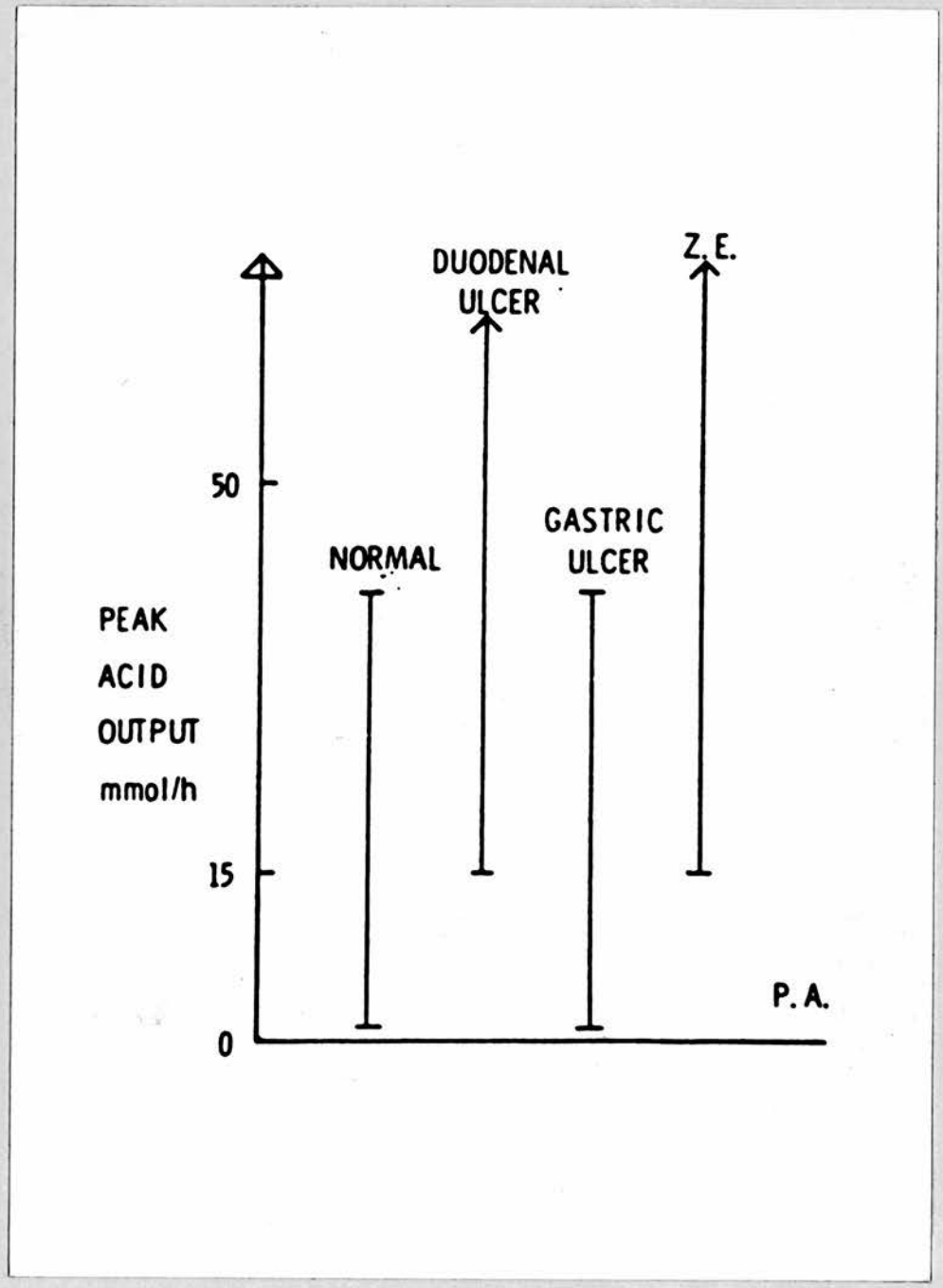


Fig 1.2 II Secretory status in health and disease



2 DESIGN AND METHODOLOGY

2.1 Rationale

From evidence cited in Ch 1.1, it is clear that demands for pharmacological and surgical intervention remain a significant burden on the health services. It has been estimated (221) that the cost in lost wages alone in the United States are between 1.3 and 2.6 billion dollars.

The types of groups of drugs, and the numbers of drugs of each type, available for the treatment of duodenal and gastric ulcer have grown in exponential fashion over the last decade. Although several - burimamide, oxmetidine, metiamide, tiotidine, loxtidine - of the H2 receptor antagonists have been withdrawn, there are even more - cimetidine, ranitidine, nizatidine, etintidine, famotidine, CM 57755, ICI 162,846 - which have become established or are in the process of establishing themselves in the market place. Some of the polycyclic drugs can claim just as long a lineage in the therapy of duodenal ulcer (147) and, with the advent of more specific antagonists of the gastric muscarinic receptors such as pirezepine, prove a viable alternative choice to the prescriber. The explosion of research into prostaglandins, especially the synthetic analogues, and the advent of extremely powerful antisecretory agents such as the substituted benzimidazole omeprazole, further expand the therapeutic options.

With this background, the traditional place of antacids has been at least displaced, if not dislodged. After it was proved (296) that antacids given in high dosage did actually accelerate the healing rate of duodenal ulcers, the subsequent tendency has been to progressively reduce the amount of antacid used (223,35,220) in attempts to establish the minimum effective dosage, especially because high doses of the

magnesium-containing compounds cause diarrhoea.

The following studies examine examples of many of the above types of anti-ulcer drugs, both in the laboratory in healthy volunteers and by monitoring the response in duodenal ulcer healing trials. The results of these studies form the basis of a discussion of current options in the therapy of duodenal ulcer.

2.2 Project Design

The basis of the thesis involves studies which cover a time-span of six years. Preliminary data from animal studies, such as in the section on prostaglandins, are presented before the data generated by studies in healthy volunteers. These clinical pharmacological investigations precede the results of clinical trials - acute healing, refractory ulcer healing and maintenance therapy. Studies involving compounds which have less of an effect on intragastric pH, such as the antacids, or a weaker anti-secretory effect, such as the polycylic drugs and prostaglandins, are presented before the more powerful anti-secretory agents such as the H2 receptor antagonists and omeprazole.

Several of the ulcer healing studies, of both acute and refractory ulcers, formed part of multicentre studies and the main authors are acknowledged at the beginning of the thesis. Where results from other centres are included for analysis, these are derived from a protocol identical to that described in the methodology.

All of the secretory studies, with the exception of the antacid study, were performed in Ninewells hospital. The methodology for the antacid study however, which was undertaken at McMaster University, closely followed that which had been followed in Dundee.

2.3 Methodology

All subjects and patients underwent detailed screening involving questionnaire, clinical examination, urinalysis, ECG and both biochemical and haematological profile - before entry to the studies. The haematology (FBC, platelets, red cell indices, white cell differential, film and ESR), the biochemistry (Urea, electrolytes, glucose, calcium, phosphate, urate, protein, albumin, bilirubin, alkaline phosphatase, AST and GGT) and the urinalysis were repeated on completion of the study. No other medication was permitted in the healthy volunteers and any anti-secretory medication taken by patients was discontinued 48 hrs before the study.

2.3.1 Nocturnal Gastric Secretion

Subjects were requested to refrain from the consumption of alcohol, caffeine-containing beverages and cigarettes for 24 hours before entry. After a light evening meal (scrambled egg, mashed potatoes, jelly and ice cream) at 1800 hrs, a 12 FG vented nasogastric tube (Argyle Catheters) was passed into the stomach at 1945 hrs. Optimal position of the tube was then confirmed by the water recovery test (159) and the gastric contents were aspirated and discarded. Continuous low pressure aspiration was then applied by means of a suction pump and gastric contents were collected in a glass measuring cylinder. The volume collected at the end of each hour was recorded and an aliquot (5-10 mls) stored at 4 degrees Centigrade for analysis of pH, acid concentration and peptic activity within 12 hrs of completion of the test.

The pH and acid concentration were determined by automatic pH meter (Radiometer Copenhagen) which titrated to pH 7.0 with 0.1N sodium hydroxide. Peptic activity was assessed using the method described by

Berstad (31). The output of acid and pepsin were calculated in mmol and mg per hour or 12 hours, as products of the volume/1,000 and the concentration of acid (mmol/l) and pepsin (mg/l) respectively.

2.3.2 Pentagastrin-stimulated secretion

Following an overnight fast, a nasogastric tube was positioned as above, gastric contents discarded and continuous low pressure suction applied. After one hour (basal), pentagastrin was administered by continuous intravenous infusion at 0.6mcg/kg/hr. Gastric contents were aspirated, measured and analysed as before. A modified duodenal tube manufactured from radio-opaque polyvinyl tubing was passed at the start of the procedure when medication was to be administered enterally (Fig 2.3 I). Thus it was possible to test the effect of a compound on pentagastrin-stimulated secretion without interrupting gastric aspiration after administration of the drug. The presence of bile-stained alkaline aspirate was taken as evidence that the tip of the tube lay distal to the pylorus and, following administration of the drug, an infusion of phenol red was commenced through the duodenal tube. Significant pyloric reflux of duodenal contents could thus be detected and, in that event, the study was abandoned and repeated on another day. After one hour, either the drug or placebo was administered through the duodenal tube on different days in random order and aspiration continued for a further one or two hours.

2.3.3 24 hour Secretory Tests

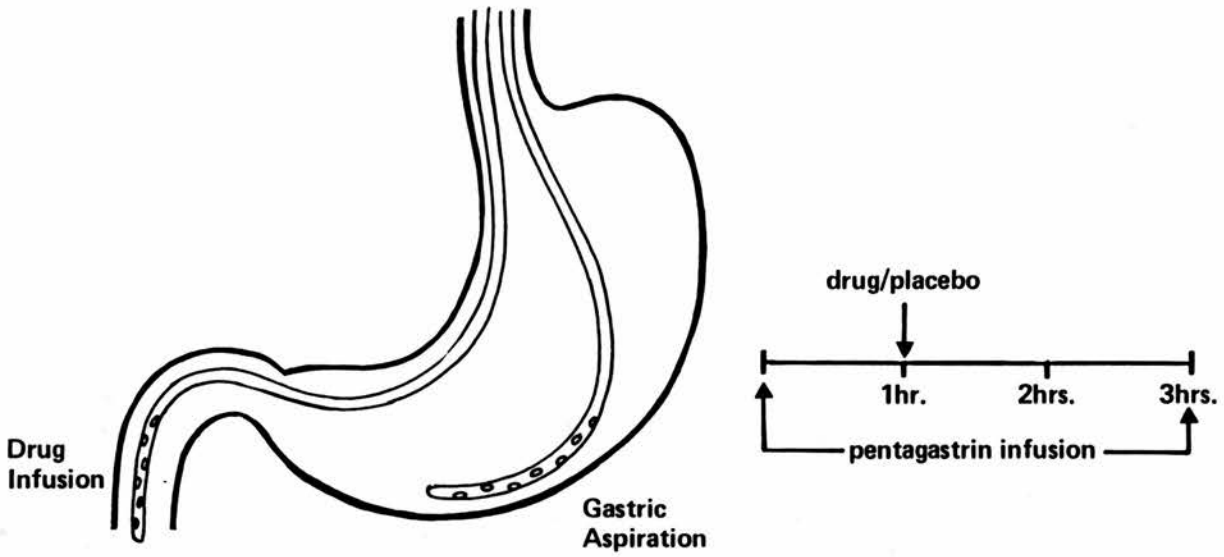
These were carried out from 2000 hrs to 2000hrs (Dundee) or 0700hrs to 0700 hrs (McMaster). Total gastric aspiration was performed in Dundee

from 2000 hrs to 0800 hrs. Then, with the nasogastric tube left in situ, the volunteers ate three standardised meals at 0800, 1200 and 1800 hrs. Aliquots of 5 mls were withdrawn hourly for estimate of H+ concentration and peptic activity.

2.3.4 Endoscopic examination

All patients attended for endoscopy at 0900 hrs, following an overnight fast. After informed consent, premedication was given with up to 20mg of diazepam intravenously and examination carried out to the second part of the duodenum with the Olympus P2 forward-viewing gastroscope. Biopsies, when taken, were obtained with the P2 forceps, which were also used to gauge the size in mm of ulcer craters.

Fig 2.3 I Tube placement for pentagastrin studies



3 ANTACIDS

3.1 Introduction and Pharmacology

Antacids are the most time-honoured of all therapies which are still in current use for dyspeptic disorders. Pliny in the first century AD and Paracelsus in the sixteenth century recommended the use of crushed coral and pearls respectively (395). The rational basis for the use of antacids in the therapy of duodenal ulcer is either for the relief of pain - the mechanism is not clearly understood but may be related to changes intragastric pH (414) - or in the belief that antacids actually alter the natural history of the disease if sufficient antacid is given to neutralise gastric acid and abolish peptic activity. Both of these viewpoints are considered in a review by Lambert (225) on the use of antacids in duodenal ulcer disease. The study by Peterson (296) was the first to demonstrate acceleration of healing of duodenal ulcer with antacids under randomised double blind conditions. Not only has the efficacy of antacids in affording relief from symptoms been questioned (370) but the dose of antacid in terms of mEq of buffering capacity which is required to accelerate the healing rate of duodenal ulcer has also been a topic of some controversy. This topic has been reviewed in editorials both by Langman (230) and Heading (162) , with particular emphasis on the optimal dose of antacid required. Several authors have demonstrated a significant advantage over placebo in the healing of ulcers with relatively low doses of antacid (223,35,220) in regimens which would clearly still permit considerable continuing intragastric peptic activity.

The publication of a fourth study (405) demonstrating the efficacy of low dose antacids in duodenal ulcer disease prompted the following study to be undertaken, seeking to establish a rational basis for these

findings in terms of intragastric acidity .

The antacid tablets used were Link 1100 (identical to those in the Weberg study) which consisted of aluminium hydroxide and magnesium carbonate in a co-dried gel. Each tablet had an acid buffering capacity of 30 mmol. The placebo tablets consisted of mannitol and sorbitol, with negligible buffering capacity.

3.2 Subjects and Modifications to Methods

The subjects were seven healthy young male non-smokers, aged from 20 to 25 years (mean 24 years). Meals were identical in timing and content on both days and, as in the Weberg study, tablets were administerd in double blind fashion four times daily - 1 hour after meals and at bedtime. The procedure for passing and positioning the nasogastric tube was as described in Ch 2.3. The pH of the gastric aspirate was determined hourly. Individual glass electrodes were used for each subject thus avoiding the risk of cross infection when the aspirate was returned to the stomach. The concentration of acid was calculated from the pH (1/antilog pH x 1000) and statistical analysis undertaken by ANOVA.

3.3 Results

Mean pH and H+ concentration on control and active therapy are shown in Tables 3.3 I and II. These results are also depicted graphically in Figs 3.3 I to IV. For purposes of analysis, each 24 hour period is broken into morning (0700-1200 hrs), afternoon (1300-1800 hrs), evening (1900-2300 hrs) and night (2400-0700 hrs). During administration of antacids there is a significant decrease in acid concentration in all time periods except during the night, with the

greatest of the decreases in the morning, although the highest value of significance was in the evening.

Table 3.3 I **pH of gastric aspirate**

24 hour period	Mean	SEM	p
Antacid	2.22	0.11	0.0097
Placebo	1.84	0.07	
% increase	21		
Morning			
Antacid	2.68	0.21	0.015
Placebo	1.76	0.09	
% increase	52		
Afternoon			
Antacid	2.29	0.08	0.0028
Placebo	1.87	0.04	
% increase	22		
Evening			
Antacid	2.49	0.13	0.257
Placebo	2.28	0.18	
% increase	9		
Nocturnal			
Antacid	1.54	0.08	0.586
Placebo	1.49	0.10	
% increase	3		

Table 3.3 II **Hydrogen ion activity**

24 hrs	Antacid	22.45	3.90	0.0186
	Placebo	37.12	5.09	
	% decrease			40%
Morning	Antacid	12.53	3.33	0.0346
	Placebo	27.48	4.14	
	% decrease			54%
Afternoon	Antacid	20.34	4.61	0.0318
	Placebo	36.39	4.47	
	% decrease			44%
Evening	Antacid	17.30	4.50	0.0044
	Placebo	33.82	5.93	
	% decrease			49
Night	Antacid	37.14	5.51	0.2473
	Placebo	49.89	9.56	
	% decrease			26%

Fig 3.3 I Effect of antacid on gastric acidity (mean hourly pH)

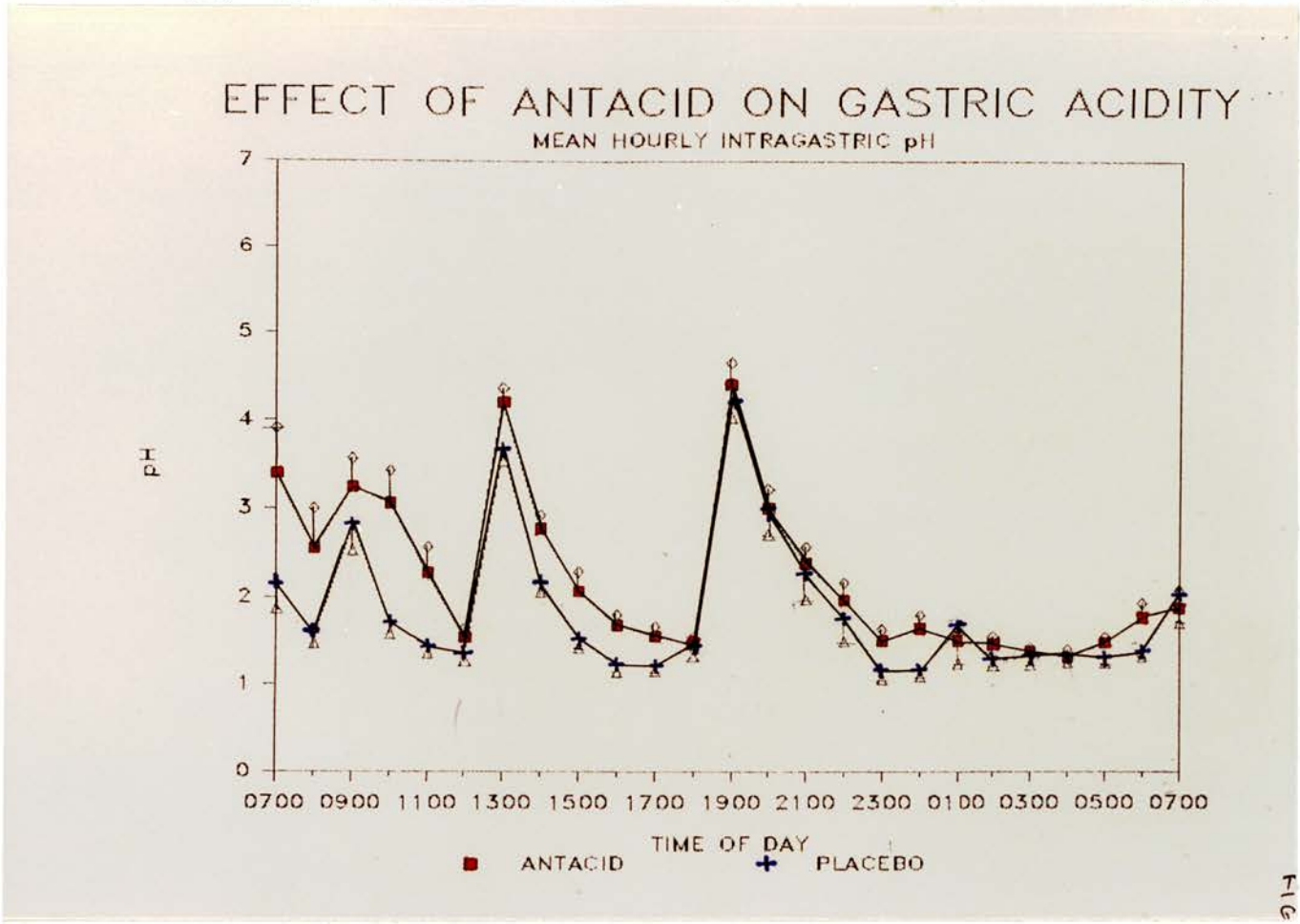


Fig 3.3 II Effect of antacid on gastric acidity (mean period pH)

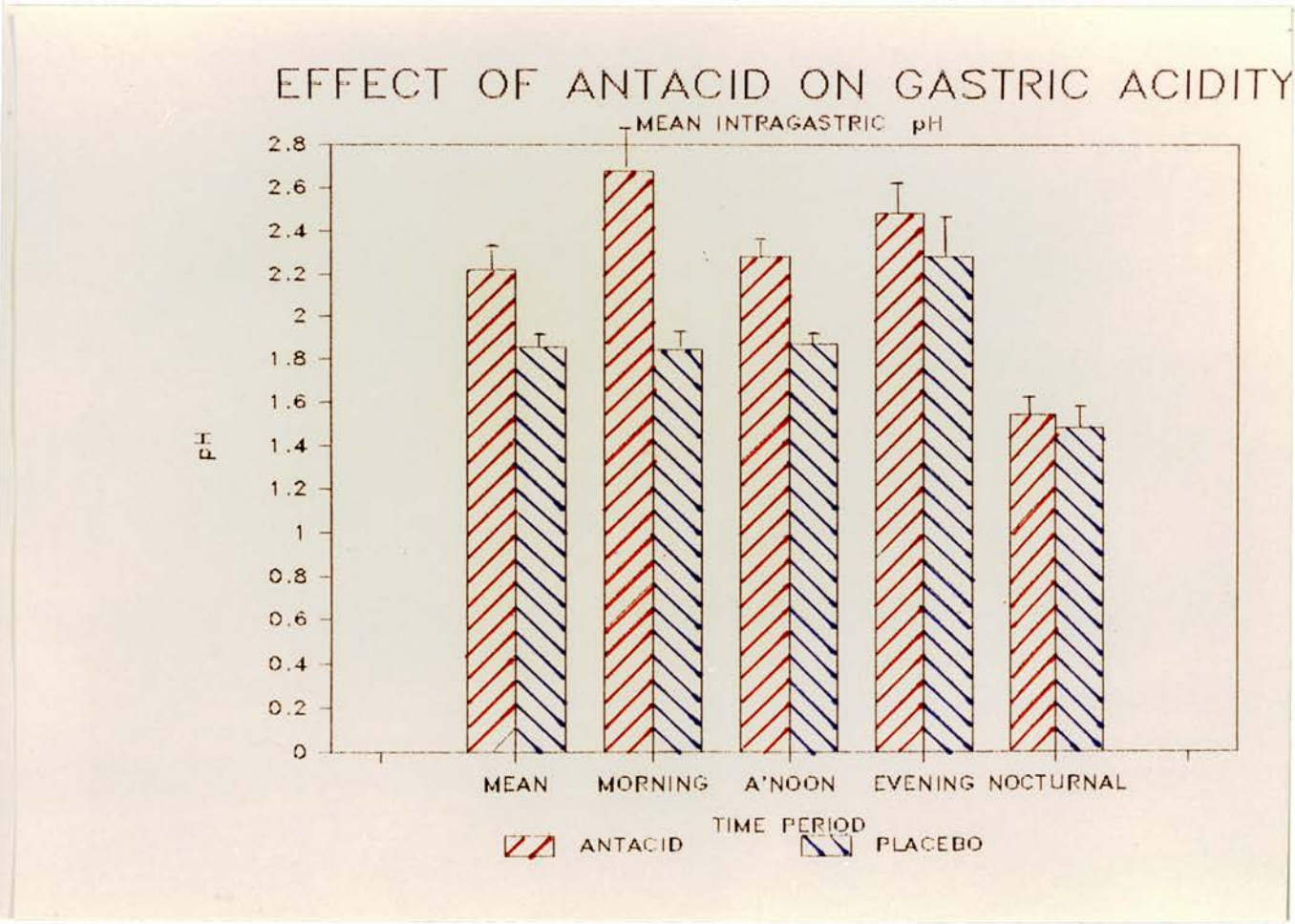


Fig 3.3 III Effect of antacid on gastric acidity (mean hourly H+)

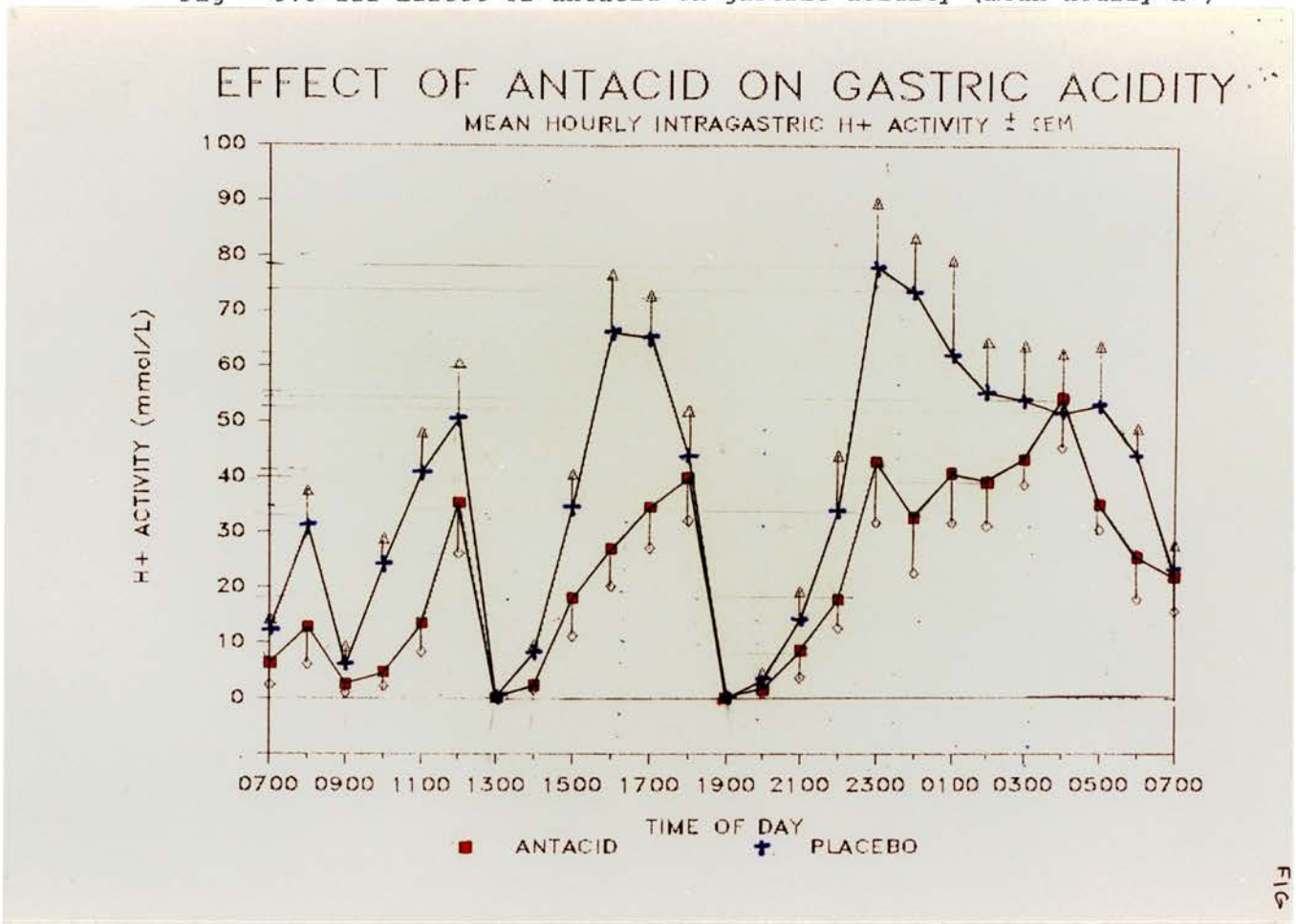
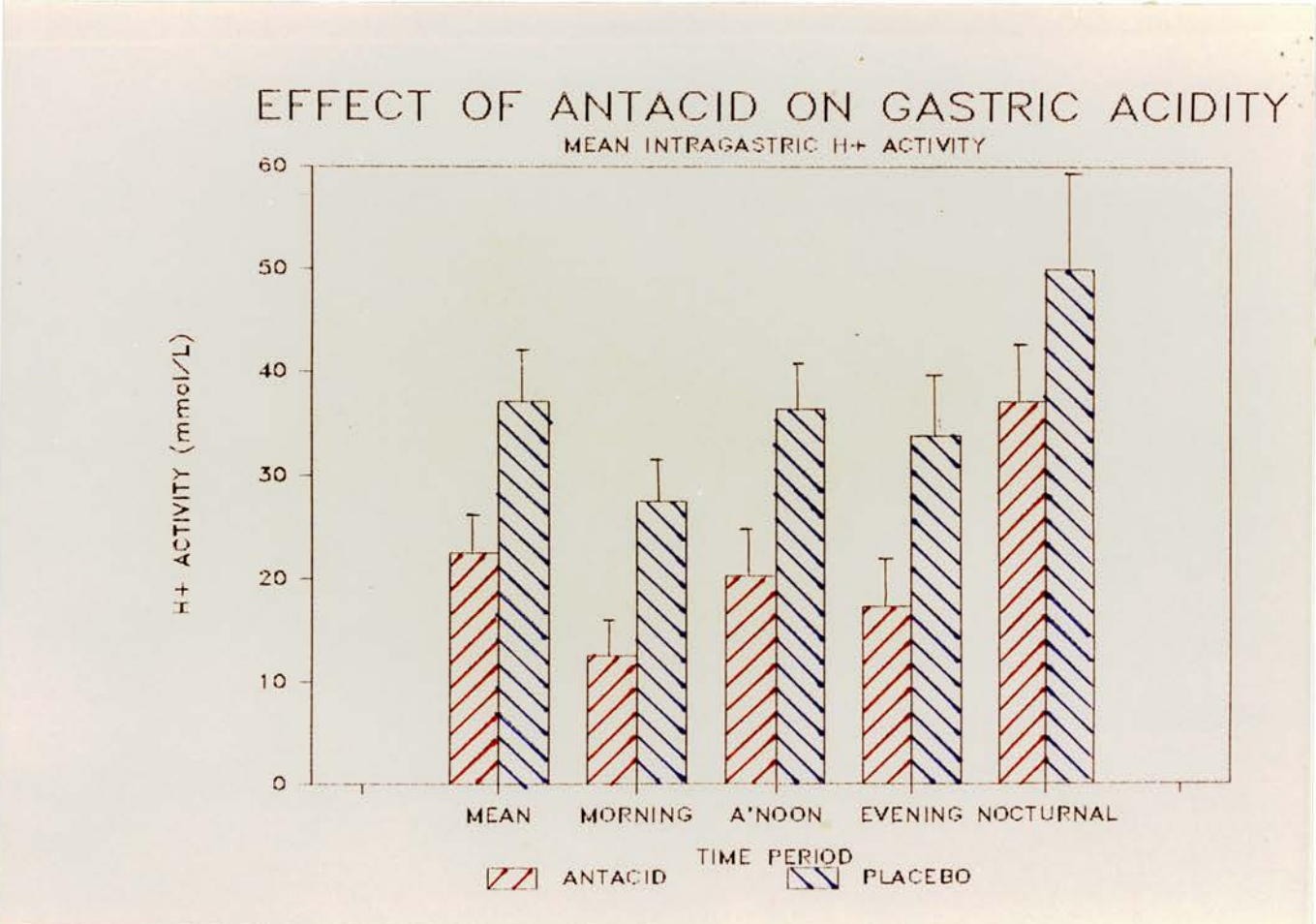


Fig 3.3 IV Effect of antacid on gastric acidity (mean period H+)



3.4 Discussion

The absence of apparent effect of one 30 mmol buffering capacity antacid tablet on nocturnal intragastric pH was less surprising than the extent of the effect of these tablets when administered post-prandially. There was a significant fall in intragastric acidity following all three meals on the active therapy day. Despite the widespread availability and use of antacids, a number of side effects have been described - hypercalcaemia, binding of other drugs, stimulation of gastrin release, binding of phosphate with resultant osteomalacia, copper deficiency and aluminium toxicity which has been linked to Alzheimer´s disease (165,8,80), although the latter is not proven (204). Not only is it important to establish the minimal effective dosage of antacid to diminish side effects, but also to reduce cost and increase compliance. Although a number of mechanisms have been invoked other than a reduction in intragastric acidity to explain ulcer healing with antacids, such as binding of pepsin, bile acids and lysolecithin (34,27), and direct cytoprotection (151,374), the reduction in meal stimulated acid demonstrated in this study may account for the acceleration in the ulcer healing rate without resorting to these other mechanisms.

4 PROSTAGLANDINS

4.1 Introduction

4.1.1 Synthesis and Biochemistry

Prostaglandins are derivatives of 20-carbon-chain unsaturated fatty acids and, as such, form part of a larger group of biological agents called the eicosanoids, together with leukotrienes, thromboxanes and lipoxins (121,160,272,343). The synthetic pathway is illustrated in Fig 4.1 I. The carbon atoms are numbered starting with the carboxyl radical, the letter (A through J) denotes changes in the ring structure and the number (1 through 3) refers to the number of double bonds in the side chains.

Prostaglandins E, F and I are present in the gastric mucosa and gastric juice, and both the synthetic and degradative enzymes of prostaglandin metabolism are present in gastric epithelium. A major stimulus to the synthesis of prostaglandins is trauma, whether mechanical or chemical (37,29,209,87,215,216,323,324). There is, consequently, an immediately apparent problem in assessing the significance of mucosal "content" of prostaglandins since this may merely be a reflection of synthesis stimulated by the process of taking the sample. In addition, the half-life of naturally occurring prostaglandins varies from a few seconds to several minutes (325). Lastly, both platelets and leucocytes are potent sources of prostaglandins. Contamination with blood and minor variations in the methodology may therefore give rise to the major differences in the levels of prostaglandins within gastric and duodenal tissue reported in different studies.

4.1.2 Mucosal prostaglandins and ulcer pathogenesis

In laboratory animals (rabbits) in which antibodies to PGE2 and 6-keto PGF1 alpha were developed, an extremely high incidence of aggressive duodenal ulcer disease was noted (285). The concept that these results might be due to an abnormally low level of tissue prostaglandins was therefore developed, but has lost ground with the finding that, in humans, there is no evidence in the duodenal ulcer population that specific serum binding to these prostaglandins exists (319).

There have been conflicting reports on the levels of prostaglandins in patients with ulceration or inflammation of the upper gastrointestinal tract. Over the last decade, there have been four reports demonstrating no change (214,5,2,210), six reports of a decrease (347,169,217,312,313,418)and three reports (161,71,338) of an increase in prostaglandin synthesis or content. Synthesis of PGE2, PGD2, TxB2, PGF2 and PGF1 alpha was reported to be similar in a group of controls to that in patients with active duodenal ulcer in the fasting state but, on feeding, synthesis increased in 5 out of 8 normals, but decreased in 8 out of 10 duodenal ulcer patients, after feeding (2). Thus, there may be primary abnormalities either in the synthesis or in the release of mucosal prostaglandins in ulcer disease but in order for progress to be made, a considerable number of methodological problems have to be overcome.

The first study, therefore, examines the relationship between "content" and "synthesis" of two prostaglandins (E2 and 6-keto F1 alpha) in biopsies of rat gastric corpus mucosa. In addition, since this problem had not previously been addressed, the effect of different sizes

of biopsy forceps on these parameters was also assessed.

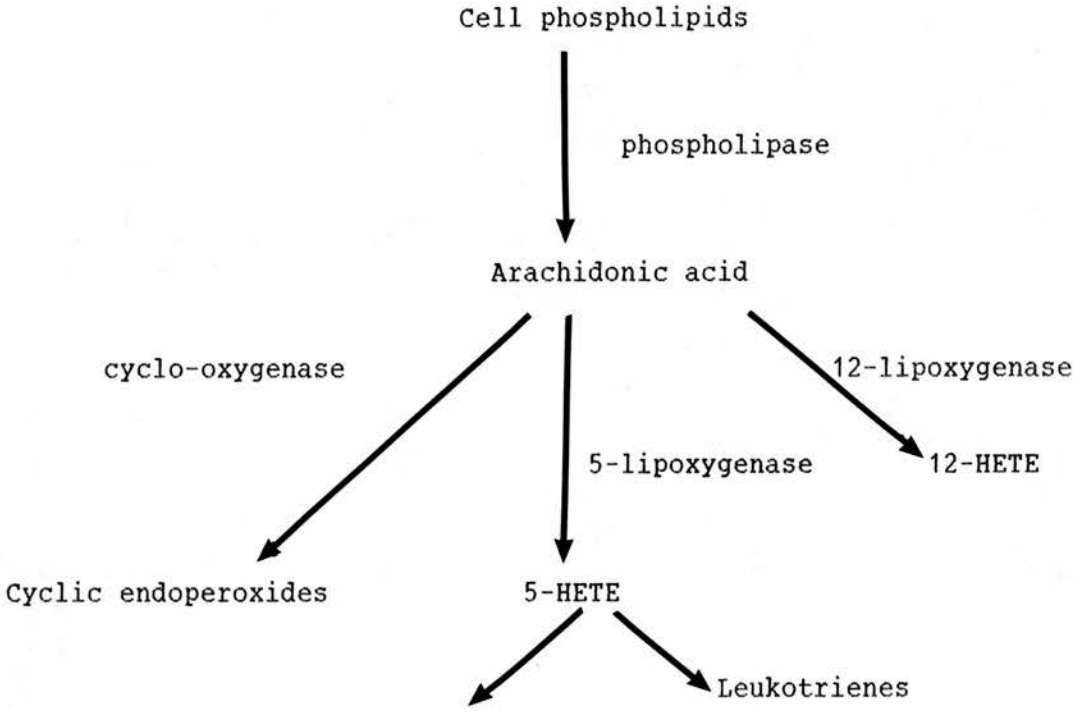
4.1.3 Exogenous prostaglandins and gastric secretion

Many of the naturally occurring prostaglandins of the E and I groups lower cyclic AMP in parietal cells (356) and inhibit gastric acid secretion (322,406). Oral PGE2 may or may not be an antisecretory agent in humans (203,211,321). The addition of a methyl group, however, reduces the rate of degradation and both Trimoprostil and Enprostil are capable of inhibiting basal, meal-stimulated and pentagastrin/histamine-stimulated gastric acid secretion (409,88,89,247). The combination of this anti-secretory action and the ability of prostaglandins to protect the sub-epithelial layers of the duodenal mucosa from damage by injurious agents such as ethanol (322) make this group of compounds theoretically very attractive in the therapy of peptic ulcer disease. With these findings in mind, it was felt to be particularly relevant to examine the anti-secretory ability of two of the synthetic prostaglandins, trimoprostil and enprostil, in healthy volunteers with particular reference to nocturnal secretion.

Table 4.1 I enumerates the healing rates obtained in endoscopically controlled double-blind trials with the synthetic prostaglandins which have been published to date. Hunt and his colleagues have analysed the healing rates of duodenal ulcer obtained with a number of compounds, including some of the synthetic prostaglandins and compared these with the ability of the compounds to inhibit the concentration of nocturnal acid (176). Not only is there a direct linear relationship between these two parameters but the same relationship exists for the synthetic prostaglandins. This suggests that the ability of the synthetic

prostaglandins to accelerate ulcer healing is related purely to the acid inhibitory component rather than to any "cytoprotective" effect.

Fig 4.1 I **Prostaglandin Synthesis**



PGD2 PGF2 PGE2 Prostacyclin Thromboxane

HETE = hydroxyeicosatetraenic acids

Table 4.1 I **Four week healing rates of duodenal ulcer with prostaglandins**

Drug	Dose	No of Trials	No of patients	% healed
Enprostil	70mcg bd	2	47	80.9
Enprostil	35mcg bd	2	252	72.2
Misoprostol	200mcg qid	2	181	69.6
Arbaprostil	100mcg qid	1	82	67.0
Trimoprostil	750mcg qid	1	30	61.0
Misoprostol	50mcg qid	2	173	43.9

References (10,58,22,234,281,57,21,389)

4.2 Mucosal Prostaglandin Content

4.2.1 Methods

All gastric mucosal samples were obtained from male Wistar rats, fasted for 24 hours and anaethetised by pentobarbital given intraperitoneally. A gastrotomy was performed, the gastric mucosa flushed gently with normal saline and three serial sets of biopsies were obtained from contiguous areas of gastric corpus with the Olympus P2 and IT forceps. Total thickness (TT) samples of the stomach were also obtained by excision biopsy.

Each set of three samples were then placed individually in three wells containing 1ml of Hanks plus 0.35% bovine albumin (HBSS). To one of the three wells was added 100 microl of BTG (an anticoagulant that blocks prostaglandin synthesis). The biopsies were transferred after ten minutes to a second set of wells, one of which contained arachidonic acid (AA), which stimulates prostaglandin synthesis. After a further ten minutes, all biopsies were transferred to a third set of wells, and prostaglandin synthesis blocked by BTG in the remaining two wells (see Fig 4.2 I).

Aliquots of the supernatant were then frozen and stored at -70 Centigrade. Assays were carried out in single batches by radio-immunoassay for PGE2 and 6-keto PGF1alpha. In order to test whether any differences observed were dependent solely on the sample size or whether the thickness of the biopsy influenced the results independently of the total weight of the biopsy (different levels of prostaglandin content might be present at different levels in the mucosa), multiple mucosal samples were taken with each biopsy technique and weighed.

Results are tabulated as shown in Tables 4.2 I, II and III and analysis undertaken by 3-way ANOVA.

4.2.2 Results

Both the variations of biopsy size (p=0.0014) and level of stimulation (p=0.0001) have a highly significant effect on prostaglandin levels. The effect of the interaction of the two variants, however, fails to reach the level of conventional significance (p=0.0636).

If an adjustment is made according to biopsy weights from Table 4.2 III a different picture emerges (Table 4.2 IV). It can be seen that, in pg/ml/mg, stimulated (AA) levels of PGE2 and 6-keto PGF1 alpha increased to the highest level for both prostaglandins in the more superficial (P2) biopsies.

Fig 4.2 I **Methodology and sequence of biopsy preparation**

1.	o	o	o
10 minutes	HBSS+BTG	HBSS+BTG	HBSS+BTG
2.	o	o	o
10 minutes	nil	nil	nil
3.	o	o	o

Table 4.2. I **6-keto PGF1 alpha (pg/ml)**

	P2			IT			TT	
	BTG	HBSS	AA	BTG	HBSS	AA	BTG	HBSS	AA
1.	1600	5970	8920	3130	5420	6610	5250	10300	8920
2.	2180	1510	6580	2480	1560	5940	8770	10260	8920
3.	1100	3000	2680	680	1480	2010	1320	4120	7320
4.	1320	700	420	3280	5560	2040	2000	7360	2280
5.	2180	4910	8590	830	6780	7740	4440	6330	8680
6.	860	2240	5920	4820	6340	8140	4410	3510	8920
7.	530	4040	7770	400	10320	12410	10690	6890	13770
8.	540	2080	7740	880	3770	6810	2000	2170	8620
9.	770	960	6420	410	1880	15110	1640	3480	6610
10	180	525	4560	200	1310	3460	260	380	3490
SD	689	1815	2711	1597	2976	4219	3401	3317	3189
x	1210	2240	6500	855	4595	6710	3205	5225	8650
Ra	180-2180	960-5970	420-8920	200-4820	1310-10320	2010-15110	260-10690	380-10300	2280-13770

Table 4.2 II **PGE2 pg/ml**

1	901	282	7072	1849	267	7842	2307	4040	8162
2	1064	135	9665	1450	304	8694	3340	1474	10265
3	226	1468	558	162	1161	994	2021	3821	3752
4	697	133	569	4682	3228	2055	2536	6486	1269
5	335	1517	11439	510	2355	16948	1007	1588	15669
6	254	83	8870	1197	2351	12715	1728	1501	15100
7	503	992	9029	735	2809	18042	4756	2384	20183
8	206	668	10621	846	1355	13507	2181	1656	16365
9	25	128	5112	35	202	7962	393	448	4219
10	88	42	6533	636	1152	11499	563	753	13003
SD	352	579	3861	1367	1108	5673	1310	1850	6299
x	430	555	6947	1030	1518	10023	2083	2415	10799
Ra	25-1064	42-1468	558-11439	35-1849	202-2809	994-18042	393-4756	448-6486	1269-20183

Results are given for each individual animal 1-10, for each biopsy size (P2, IT and TT), at each level of stimulus (BTG, HBSS and AA) with Mean (x), Standard Deviation (SD) and Range (Ra).

Table 4.2 III **Weights of mucosal biopsies (mg)**

TT	IT	P2
5.8	5.2	2.2
7.0	7.5	2.4
7.3	10.4	2.6
8.7	12.6	3.2
8.8	12.8	4.2
8.9	12.9	4.7
9.1	15.9	4.9
12.3	17.8	5.4
12.3		6.1
12.9		
14.2		
14.3		
14.6		
Median 9.1	12.7	4.2
Mean 10.4	11.9	4.0
Range 5.8 - 14.6	5.2 - 17.8	2.2 - 6.1

Table 4.2 IV **Prostaglandin levels pg/ml/mg biopsy**

F1 alpha

P2			IT			TT		
BTG	HBSS	AA	BTG	HBSS	AA	BTG	HBSS	AA
281.5	705.6	1490.0	143.8	373.3	590.5	392.1	526.9	745.5

E2

108	139	1737	87	128	842	200	232	1038

4.3 Trimoprostil

4.3.1 Introduction and Pharmacology

Trimoprostil (11R,16,16-trimethyl-11-desoxy prostaglandin E2) is a PGE2 analogue (Fig 4.3 I) which, in studies on inhibition of basal gastric secretion in the rat, has been reported to be approximately 2,000 times more potent than cimetidine on a molar basis (124). Further animal experiments have shown that it is effective in preventing duodenal ulcers caused by pyloric ligation, stress or indomethacin (124). Approximately half of an oral dose is absorbed from the stomach and the drug is almost totally excreted in bile. Maximum plasma concentration is achieved in 45 mins, but this is delayed to 130 minutes if administered after food (407). In studies of healthy volunteers, the IC50 of circulating trimoprostil for basal acid secretion was 1.25 ng/ml, and 70-80% inhibition was achieved with serum concentrations of 3-4 ng/ml (407). Up to 60% reduction of meal-stimulated acid output was obtained in duodenal ulcer patients with evidence of a dose-response (237). In order to further define the anti-secretory effects of the drug, the inhibitory activity of two doses of trimoprostil on 12 hour nocturnal secretion of acid and pepsin has been compared with placebo in healthy volunteers.

4.3.2 Modifications to Methods

The studies were performed in eleven healthy male volunteers (students and laboratory staff) who all had acid outputs of greater than 40mmol/12 hrs, with at least five days between tests. Identical capsules containing trimoprostil (1.5 or 3.0mg) or placebo were administered under supervision at 1800hrs with a standardised light evening meal.

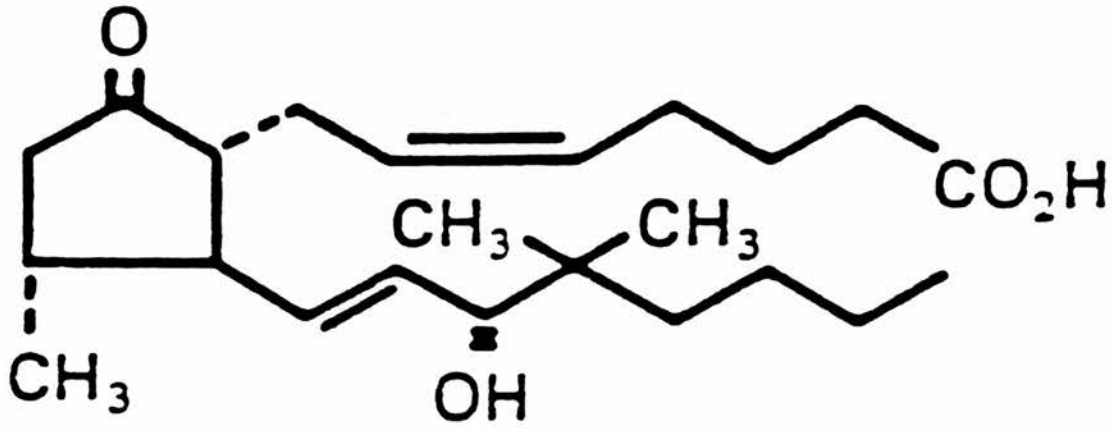
4.3.3 Results

Overnight secretion of acid was reduced from 106mmol to 68.4mmol by trimoprostil 1.5mg and to 49.4 by 3.0mg trimoprostil. Both decreases were highly significant ($p < 0.01$) and the inhibition by the two doses of the drug were significantly different ($p < 0.02$) from each other (Fig 4.3. II). On an hourly basis, the inhibition of acid secretion by 1.5mg was significant until midnight, and from 0100-0200hrs ($p < 0.01$), while the decrease with 3mg was significant ($p < 0.01$) until 0100hrs and remained significant ($p < 0.05$) until 0300hrs. When expressed as a percentage of the placebo value (Fig 4.3 III), the reduction in acid output was greater than 50% until 0200 hrs, after treatment with trimoprostil 3mg.

The reduction in nocturnal output of acid was mainly attributable to a decrease in the secreted volume of gastric juice (Fig 4.3. IV) since a significant reduction in acid concentration (Fig 4.3. IV) only occurred from 2100 to 2300 hrs with 1.5mg and from 2000 to 0100 hrs with 3.0mg ($p < 0.05$). The changes in pH were not large and in only one individual did trimoprostil increase the pH values to greater than 2 during the night (Fig 4.3. VI).

Nocturnal secretion of pepsin was significantly reduced ($p < 0.01$) from 2000 to 2200 hrs after 1.5mg trimoprostil and from 2000 to 0100 hrs after 3.0mg (Fig 4.3. VII). The nocturnal pepsin output after 3.0mg was significantly less than placebo ($p < 0.05$).

Fig 4.3 I Structure of trimoprostil



11-Methyl, 16, 16 Dimethyl PGE_2
(Roche, RO 21-6937, Trimoprostil)

Fig 4.3 II Median acid output on trimoprostil/placebo

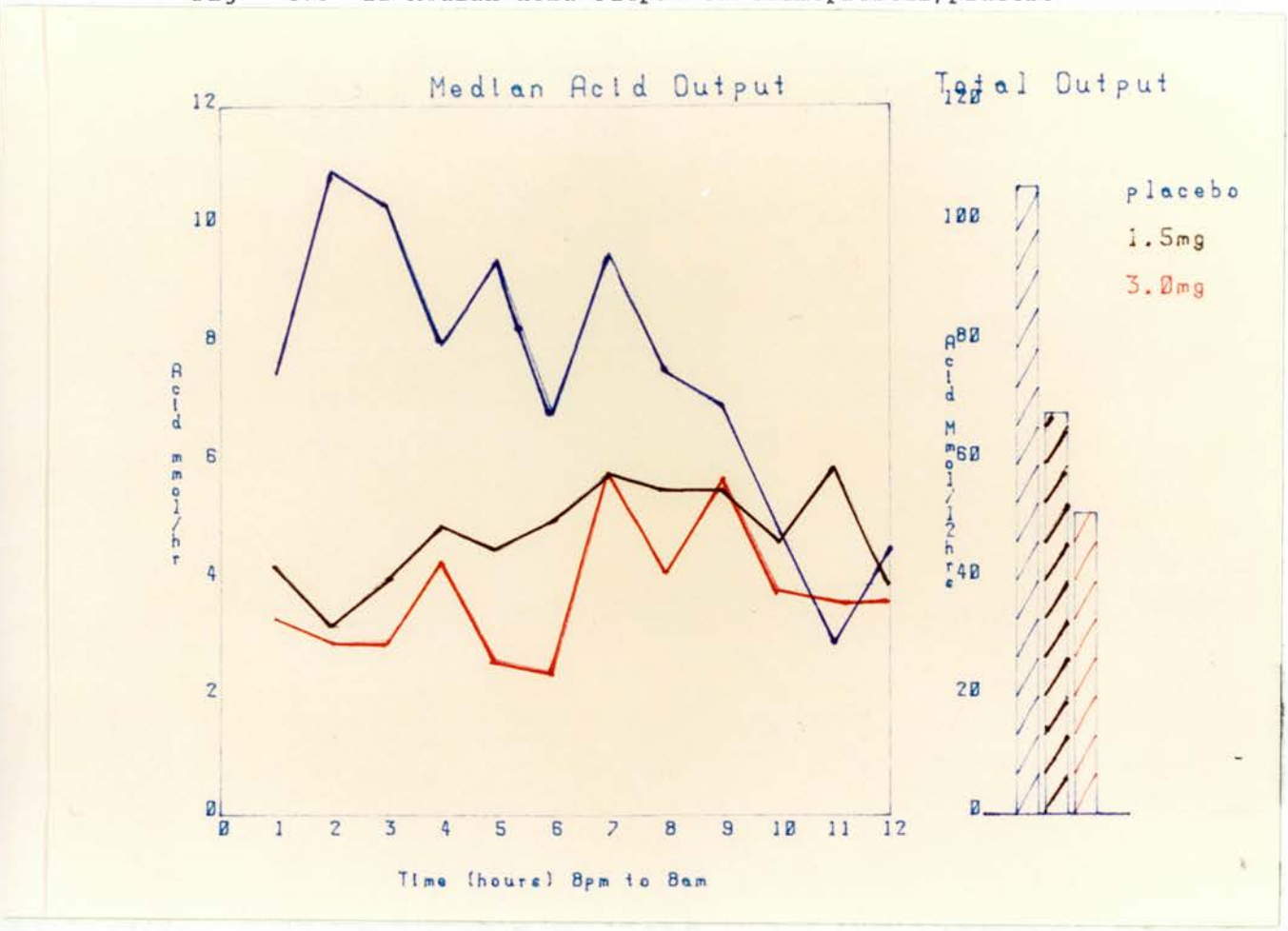


Fig 4.3 III Acid output as % of placebo on trimoprostil

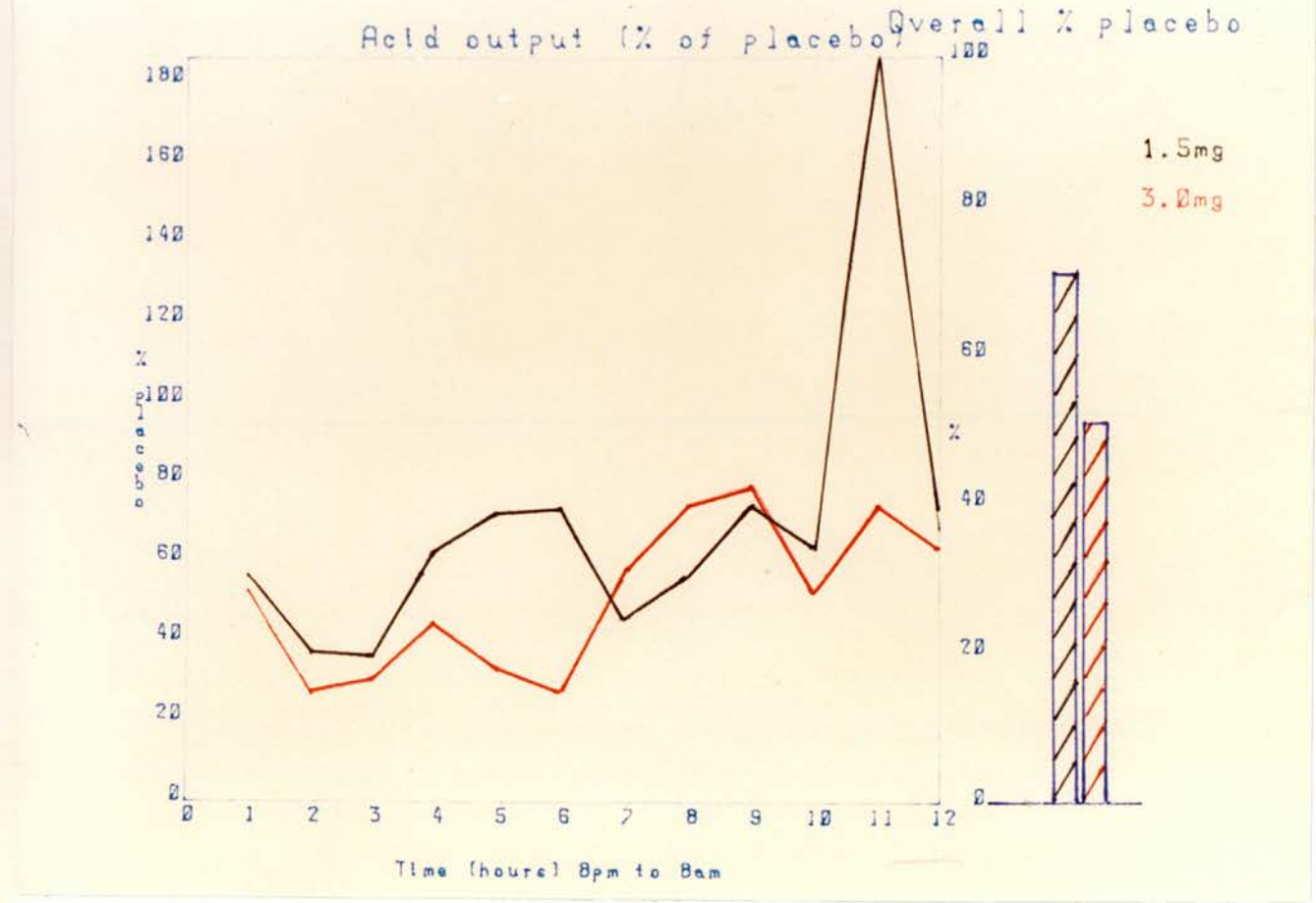


Fig 4.3 IV Volume of gastric output (mls) on trimoprostil/placebo

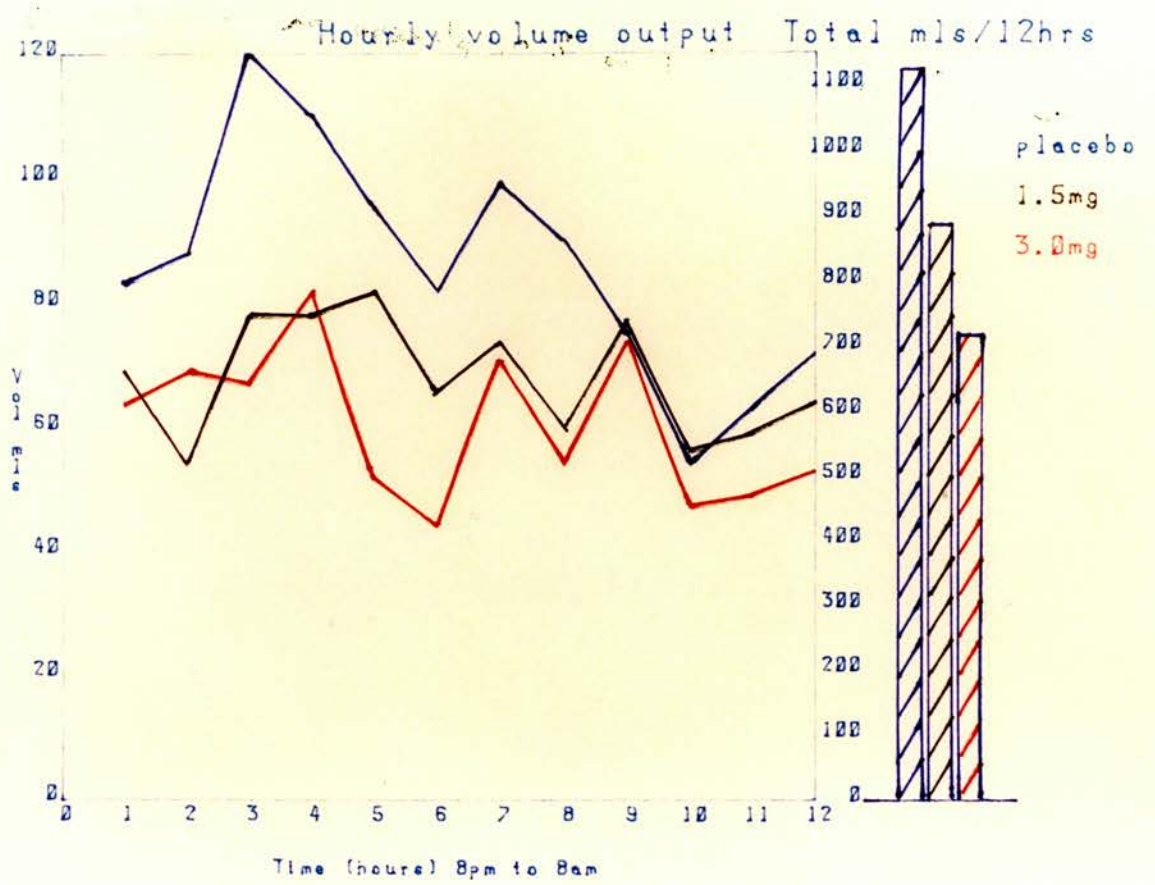


Fig 4.3 V Median acid concentration (mmol/l) on trimoprostil/placebo

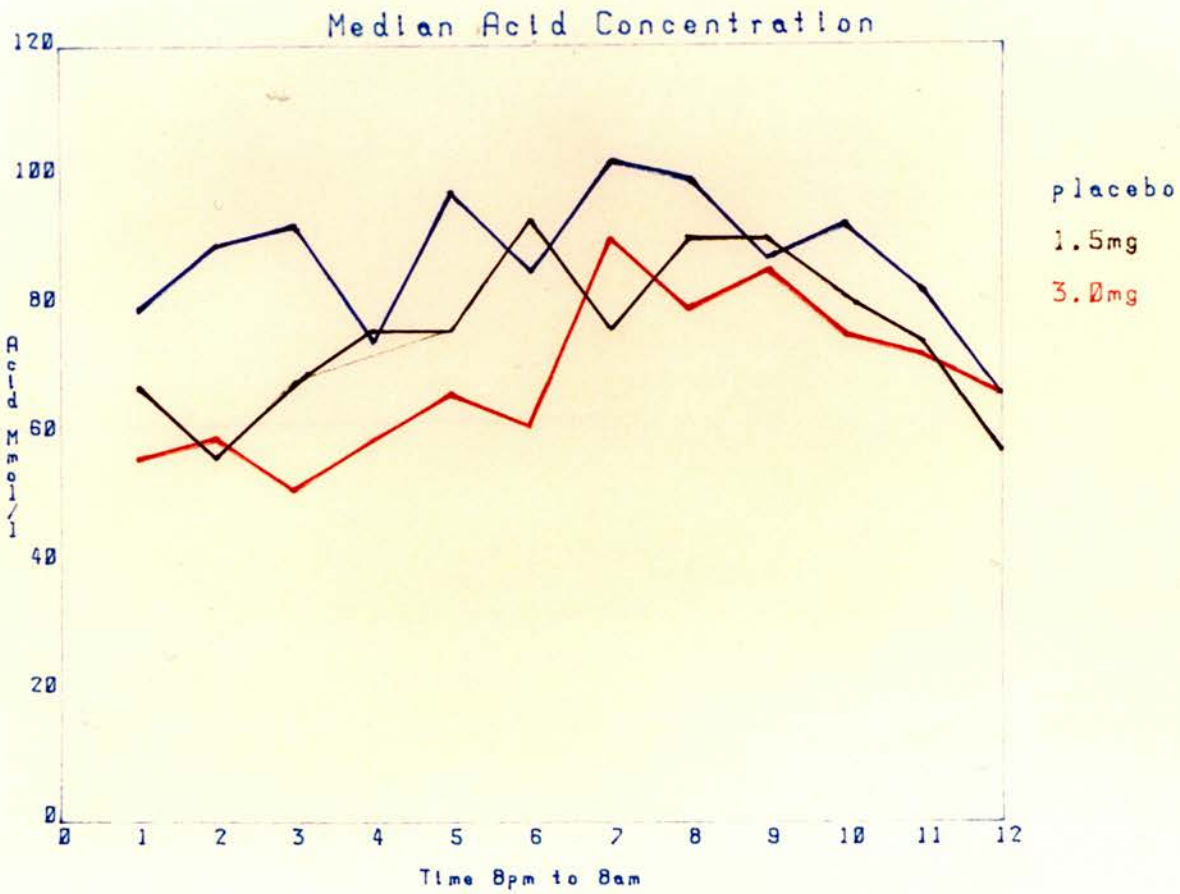


Fig 4.3 VI Hourly pH on trimoprostil/placebo

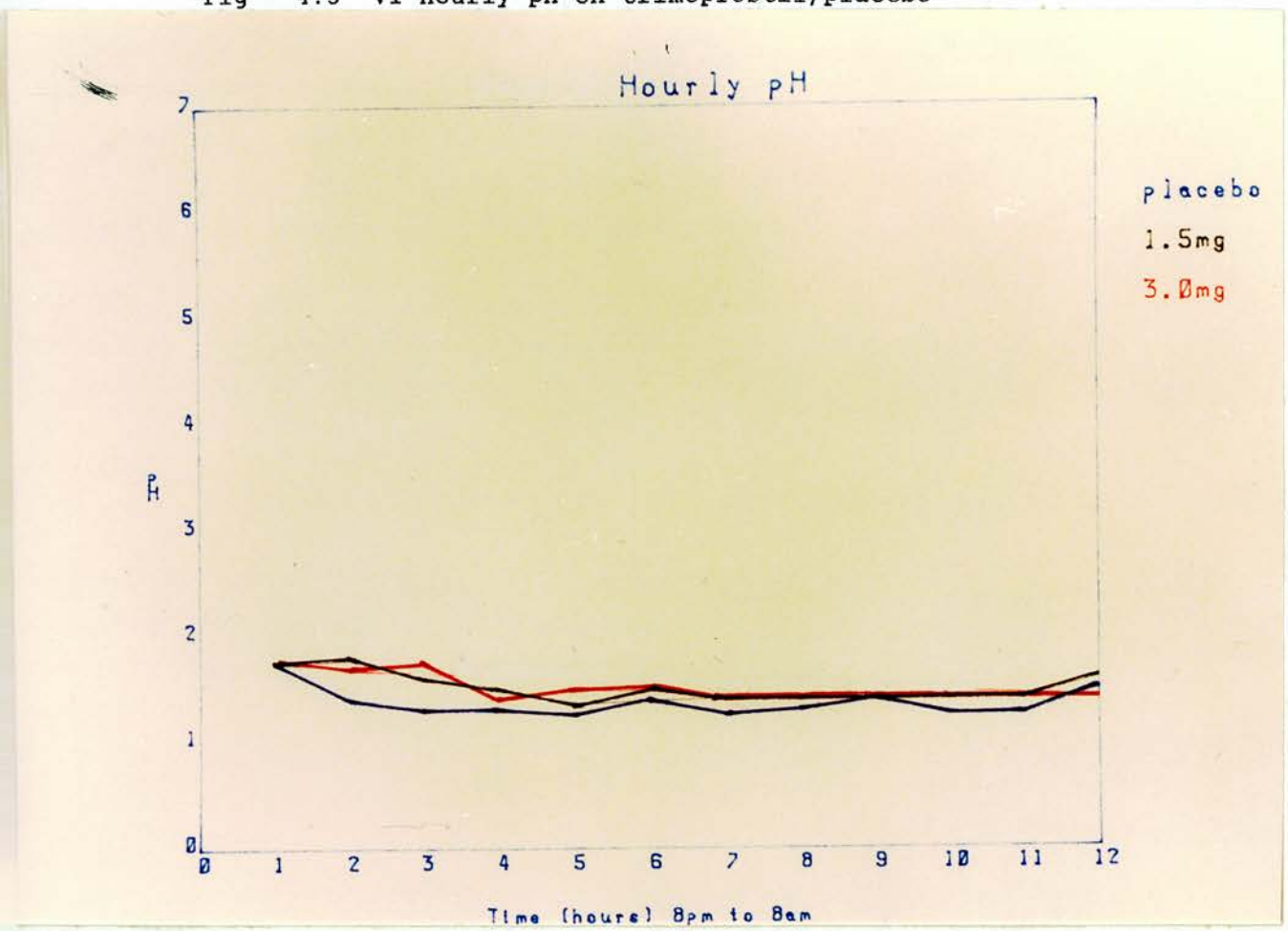
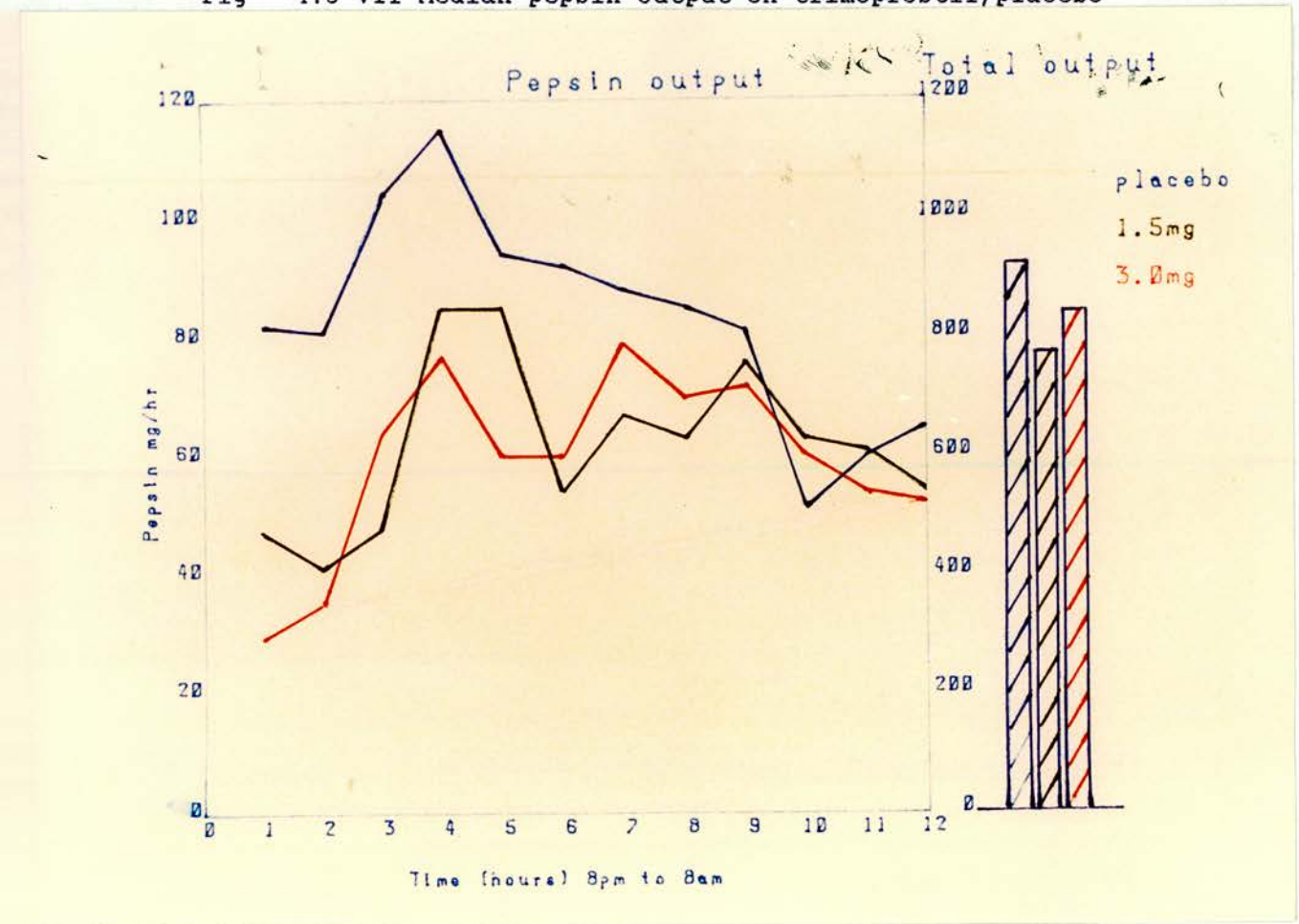


Fig 4.3 VII Median pepsin output on trimoprostil/placebo



4.4 Enprostil

4.4.1 Introduction and Pharmacology

Enprostil is a synthetic dehydro prostaglandin E2 derivative with a molecular weight of 400.45 and structure as shown in Fig 4.4 I. In the rat model, enprostil at doses of below 7.5 micro g/kg inhibited acid secretion during histamine stimulation and was approximately 300 times more potent than the naturally occurring PGE2. From isotopically labelled studies in man (345), the drug and related major metabolites have a plasma half-life of 1.75 hours. Approximately 55% is recovered in urine, the remainder being excreted in the faeces.

The purpose of this study was to examine the effect of enprostil on nocturnal secretion and to compare this with ranitidine in a group of healthy volunteers, in order to assess the potential for the treatment of ulcer disease.

4.4.2 Modifications to Methods

Eleven healthy male volunteers, age 22 (18 - 25) yrs (mean and range), underwent four separate 12 hour overnight gastric secretory studies from 2000 to 0800 hrs. Only subjects with an overnight acid output of > 30mmol and < 80mmolwere recruited. Subjects were randomised into the following treatment groups according to a Latin square pattern:

1. two capsules placebo, one tablet placebo x2
2. one capsule placebo, one capsule enprostil 35mcg and one tablet placebo x2
3. two capsules enprostil 35mcg, one tablet placebo (evening)
   two capsules placebo, one tablet placebo (morning)
4. two capsules placebo, one tablet ranitidine 150mg x2

Each treatment was taken twice daily. Thus, the four treatments

consisted of placebo, ranitidine 150mg bd, enprostil 35mcg bd and enprostil 70mcg nocte. Each treatment was taken for one week, with a minimum of one week between studies.

4.4.3 Results

Volume, acid output and pepsin output are shown in Table 4.4. I and II and are illustrated graphically in Figs 4.4. II and III. The entire data set has been analysed. The only significant change is reduced acid output with ranitidine ($p < 0.05$). The data have also been analysed following exclusion of subjects 2 and 4 (Table 4.4 II) since, according to the initial entry criteria, they should not have been included because their nocturnal acid output wa too low. Although, on repeat analysis, statistically significant change at the 5% level does not occur with any criterion other than with acid output on ranitidine, a decrease of 28% in acid output occurs following enprostil 35mcg bd and of 21% following enprostil 70mcg nocte. Pepsin output was not altered by any of the drug regimens. The rate of secretion was reduced by ranitidine by 40% and by about 20% with both dosage schedules of enprostil.

Table 4.4. I **Individual nocturnal outputs - acid, pepsin and volume**

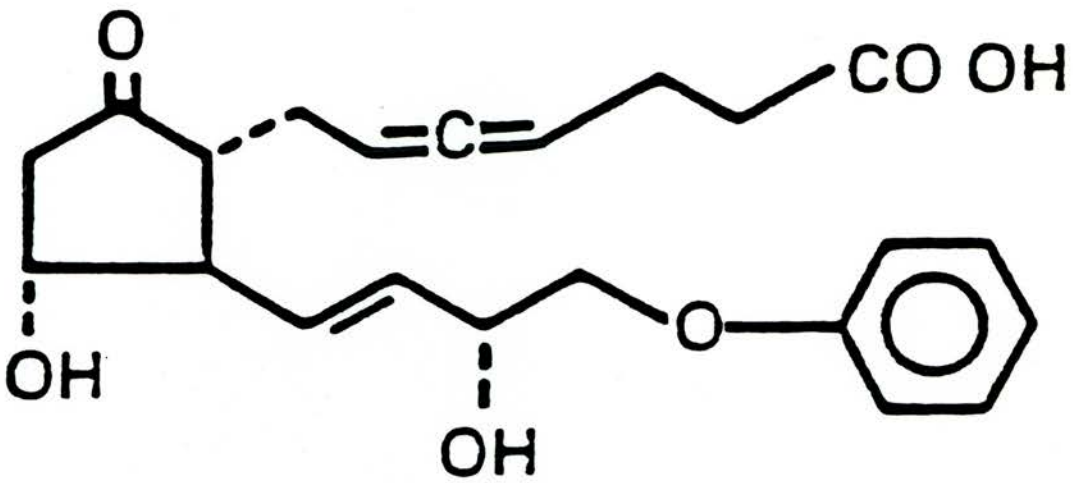
Subject	Drug	Acid (mmol)	Pepsin (mcg)	Volume(mls)
1	P	47.1	195	1962
	R	10.2	102	169
	E35	9.3	95	680
	E70	28.2	448	878
2	P	12.1	403	782
	R	4.6	62	446
	E35	5.7	139	586
	E70	37.0	599	950
3	P	29.8	684	964
	R	5.1	224	854
	E35	10.7	322	706
	E70	36.1	671	970
4	P	101.1	1902	1148
	R	15.8	430	610
	E35	74.6	1255	974
	E70	152.8	1794	1430
5	P	30.7	291	542
	R	25.5	253	526
	E35	30.2	476	752
	E70	34.6	332	552
6	P	59.2	922	836
	R	27.9	1164	702
	E35	11.5	986	510
	E70	40.1	712	770
7	P	39.0	843	1100
	R	34.4	817	644
	E35	50.9	1052	860
	E70	36.8	579	628
8	P	39.9	479	730
	R	16.6	404	496
	E35	53.8	514	748
	E70	29.0	288	456
9	P	36.6	519	614
	R	22.5	778	489
	E35	37.6	976	876
	E70	27.8	482	548
10	P	69.1	708	780
	R	25.4	704	510
	E35	40.3	536	502
	E70	61.0	573	770
11	P	73.5	790	1006
	R	31.4	805	680
	E35	59.5	991	1094
	E70	43.7	686	950

Table 4.4 II **Mean nocturnal output**

		Acid (mmol)		Pepsin (mcg)		Volume (ml)	
Mean	P	48.9		703		951	
	R	19.9	(59)	522	(26)	564	(41)
	E35	35.0	(28)	667	(5)	753	(21)
	E70	47.9	(2)	651	(7)	809	(15)
Excl. Subjects 2 and 4							
Mean	P	47.3		603		948	
	R	22.1	(53)	583	(3)	563	(40)
	E35	33.9	(28)	660	(+9)	747	(21)
	E70	37.5	(21)	530	(12)	724	(24)

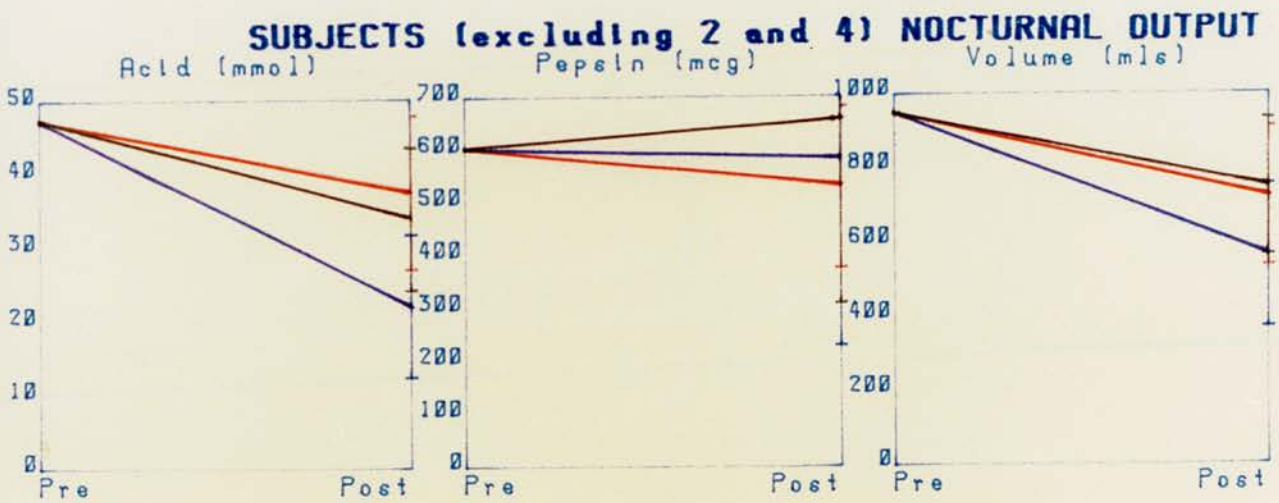
% change in parentheses

Fig 4.4 I Structure enprostil



RS-84135, Enprostil (Syntex)

Fig 4.4 II Output of acid (mmol), volume (mls) and pepsin (mg) on enprostil/ranitidine/placebo excl. subj 2 and 4



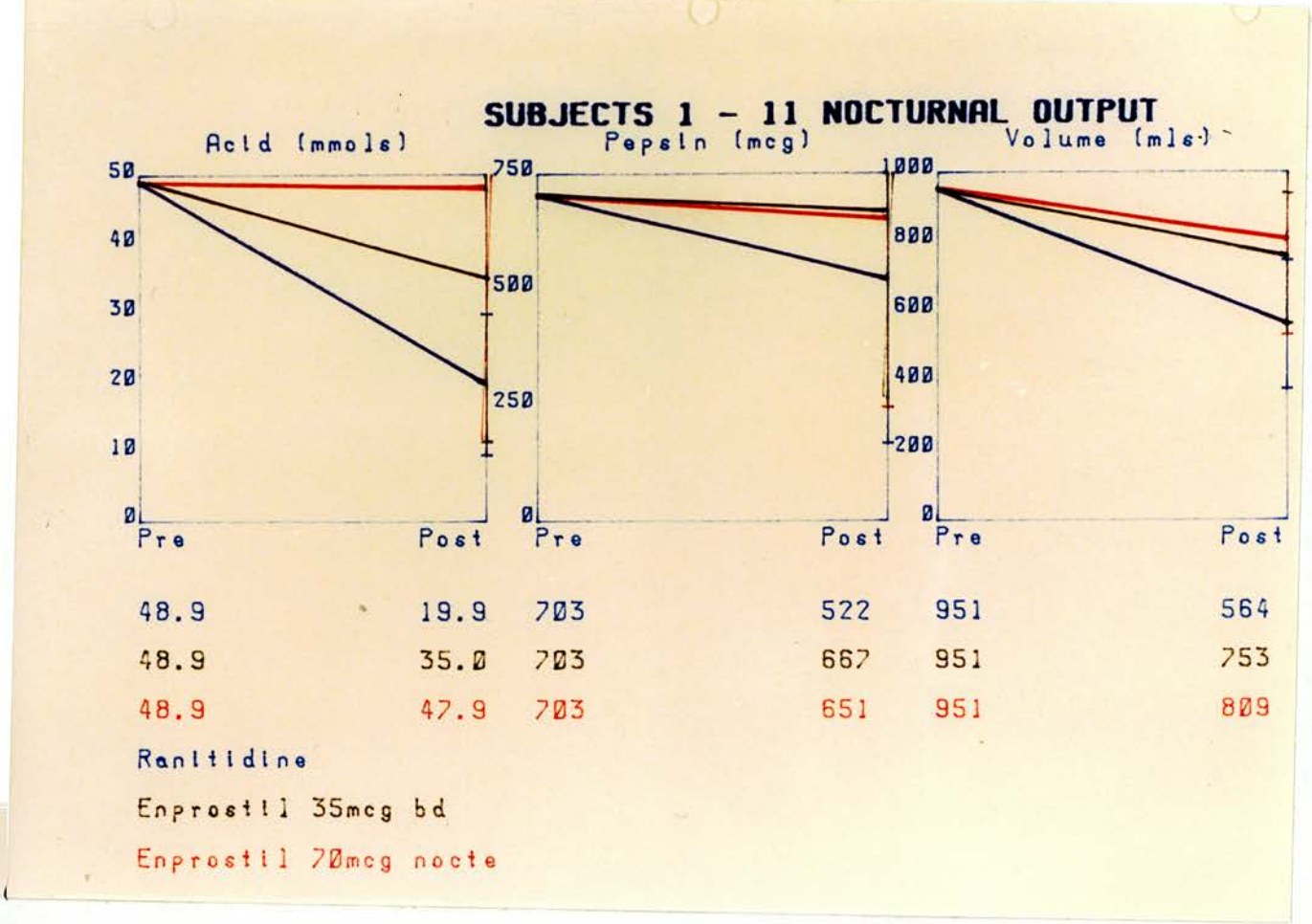
47.3	22.1	603	583	948	563
47.3	33.9	603	660	948	747
47.3	37.5	603	530	948	724

Ranitidine

Enprostil 35mcg bd

Enprostil 70mcg nocte

Fig 4.4 III Output of acid (mmol), volume (mls) and pepsin (mg) on enprostil/ranitidine/placebo subj 1 - 11



4.5 Discussion

4.5.1 Mucosal prostaglandin content

Radioimmunoassay is a sensitive, reproducible and widely-used technique with which, however, it is difficult to allow for biologically active metabolites. Considering the rapidity and ubiquity of the prostaglandin cascade, this is a major disadvantage. Within this limitation, the initial part of this study has demonstrated statistically significant differences not only between the different levels of activity (BTG/HBSS/AA) but also between different biopsy sizes. Care must therefore be taken when comparisons are made between the results of different groups of workers. One cannot assume that, simply because results are expressed per mg wet tissue weight, that the effect of different biopsy sizes is compensated for - clearly the level to which the tissue is biopsied is just as important as the size of biopsy. It is therefore recommended that comparisons only be drawn between mucosal prostaglandin levels from different studies if the level of stimulation of prostaglandin synthesis, the assay technique and the biopsy technique are all identical.

Although a wide range in the values was observed, the potential contribution by this scatter throughout the ten animals to the apparent differences observed was tested as part of the 3 way ANOVA, but was found not to contribute to the level of significance obtained.

4.5.2 Trimoprostil

The second study, with trimoprostil, shows that this compound is a moderate inhibitor of gastric secretion of acid and pepsin at doses of 1.5 and 3.0mg in healthy volunteers whose acid outputs are within the range that one might expect to find in patients with duodenal ulcer. In a dose of 0.75mg four times daily in duodenal ulcer patients, a four

week healing rate of 62% has been achieved (21). It seems likely that the gastric inhibitory effects of trimoprostil account for the ulcer-healing action of the drug. Diarrhoea has been a troublesome, dose-related side effect with some of the other prostaglandin analogues. No side effects were noted by the volunteers in this study, although single dosing might be insufficient to detect this symptom.

Any advantage which this group of compounds might present over currently available anti-ulcer therapy seems more likely to lie in the area of ulcer prophylaxis of sub groups in the population who are at risk e.g. the elderly taking non-steroidal anti-inflammatories drugs, or in the maintenance of ulcer remission.

4.5.3 Enprostil

The findings in the third study are in accord with Pounder,s study on enprostil (334). Nine patients with duodenal ulcer, in remission, were studied on three occasions - before, and on the seventh day of therapy with enprostil 35mcg bd and enprostil 70mcg nocte. Twenty four hour and nocturnal intragastric acidity was reduced by both regimens by 28% and 29% respectively . In this study also, medication was well tolerated except by one patient, who developed self-limiting diarrhoea. The Haslar group (91) also examined a group of nine duodenal ulcer patients after pre-dosing for two days with enprostil 35mcg bd and 70mcg nocte. Twenty four hour intragastric acidity was reduced by 39% and 33% respectively, and nocturnal acidity by 60% and 67%. Conceivably, if the trophic action of enprostil does counteract the anti-secretory effects, then two days of pre-dosing may be insufficient for this trophic action to occur. In the study carried out by Pounder and in the Haslar study the evening medication was given later - 2215 and 2300 hrs

- and this may account for the increase in the degree of nocturnal suppression in the Haslar study.

As one might expect from the relatively weak anti-secretory activity of this compound, duodenal ulcer healing studies have been disappointing. Bardhan (22) found that enprostil 35mcg bd healed only 46% of duodenal ulcers in four weeks, compared with 93% given ranitidine ($p < 0.01$). In gastric ulcer, however, efficacy seems to be comparable with H2 receptor blockade. Using a higher dose of 70mcg bd, Morgan et al (275) found that, of 48 patients with gastric ulcer randomised to either ranitidine (R) 150mg bd or enprostil (E), after one month 63% (E) and 50% (R) had healed, after two months 91% (E) and 83% (R) and after three months 96% (R). No significant difference was found between the two groups. No anti-secretory data are available using 70mcg bd but, since 70mcg at night did not result in greater nocturnal inhibition than 35mcg, it seems likely that the relatively greater efficacy of enprostil in gastric ulcer is due to some mechanism other than an increased anti-secretory effect.

5 POLYCYCLIC DRUGS

5.1 Mianserin, Trimipramine and Quisultidine

5.1.1 Introduction and Pharmacology

The molecular structures of these three compounds are shown in Fig 5.1 I. Quisultidine, which has not been marketed in the UK, is absorbed orally with a peak plasma concentration time after dosing of 1.6 hrs (1.0-2.5 hrs). The elimination half life is variable (1.75-20.0 hours) with a mean of 7.7 hours (385). Mianserin is readily absorbed from the gastrointestinal tract and 70% is excreted by first pass metabolism in the liver through hydroxylation, N-oxidation and N-demethylation. The plasma concentration curve is biphasic and maximal concentration is achieved 2 hrs post dose. Mianserin is excreted almost exclusively as metabolites in the urine, and has an elimination half life of between 7.7 and 19.2 hrs (257). There is some evidence that this may be significantly prolonged in the elderly (346). Trimipramine is readily absorbed following oral dosing (as trimipramine maleate), is extensively plasma bound and is excreted mainly in the urine (88). Following intravenous administration, the elimination half life is approximately 23 hours (1). Twice daily dosage would therefore be quite feasible without marked fluctuations in plasma levels.

In 1976 Guldahl (147) reported that many patients with duodenal ulcer suffered from mild depression. When trimipramine was used to treat this depression, it was noted that the rate of ulcer healing increased. Subsequently, it was shown that trimipramine increased the rate of healing of both duodenal (268,25,246,388) and gastric (388,386) ulcers, and that continued treatment induced sustained remission in many

patients with ulcer disease (387). Additional studies (327,279) showed that trimipramine inhibited gastric secretion, an effect considered relevant to the therapeutic efficacy of the drug.

Boyd and Wormsley (50) demonstrated that the new polycyclic quisultidine (LM 24056) was a powerful inhibitor of gastric secretion, so that it seemed relevant to compare the effects of three different polycyclic drugs on gastric secretion to determine whether gastric inhibition was a consistent property of this type of compound. As it was found that mianserin was a gastric secretory inhibitor, eight patients were entered into an open, pilot, ulcer-healing study.

The only polycyclic drug in common current use in the treatment of duodenal ulcer disease is pirenzepine. A review was therefore undertaken of the actions, side effects and efficacy of pirenzepine in duodenal ulcer therapy.

5.1.2 Subjects and Modifications to Methods

Overnight and pentagastrin-stimulated gastric secretion of healthy male volunteers (18-30 years) was studied. With quisultidine, a variable dose study of overnight gastric secretion was also performed in patients with duodenal ulcer. Subject numbers and dosage schedules are detailed in Table 5.1. I.

After collection of basal secretion for 30mins, an intravenous infusion was commenced with pentagastrin 2mcg/kg/hr. After one hour, either the drug (crushed and dissolved in 20mls saline) or placebo (20mls saline) was administered through the duodenal tube on different days in random order and aspiration continued for a further hour. The methodology for the overnight studies, measurement of acid and pepsin and statistical analysis were unchanged from previous studies.

5.1.3 Results

The secretion of acid in response to pentagastrin was inhibited by all three drugs in the doses used in this study (Table 5.1 II). The output of pepsin was inhibited by mianserin and quisultidine but increased by 12% after administration of trimipramine.

Overnight secretion of both acid and pepsin was inhibited by mianserin and quisultidine, but the output of both these components increased after trimipramine (Table 5.1 III). No significant adverse reactions were noted during the study. After quisultidine 300mg, most of the subjects experienced dryness of the mouth. Compared with control nights, some of the individuals slept better after mianserin and were more drowsy on the morning following the test.

Endoscopy revealed that seven of the eight duodenal ulcer had healed patients after administration of mianserin 60mg at night for four weeks.

Table 5.1 I **Subject numbers and Dosage Schedules**

Drug	Overnight Secretion (no. of subjects)	Pentagastrin Study (no. of subjects)	Dose mg
Trimipramine	7	6	50
Mianserin	9	7	60
Quisultidine	5	5	200
Quisultidine (d.u.)	23		100
			200
			300

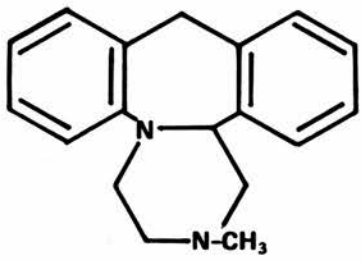
Table 5.1 II **Inhibition of pentagstrin-stimulated acid secretion**

	Acid Output (mmol ± SEM)				Pepsin Output (mg ± SEM)			
	Control	Drug	Change	p	Control	Drug	Change	p
Trimipramine	28.5±3.5	24.8±4.4	-13%	ns	156±25	175±35	+12%	ns
Mianserin	22.6±2.3	14.0±2.7	-38%	<0.01	143±19	86± 6	-40%	<0.01
Quisultidine	23.3±5.5	16.7±3.6	-29%	<0.01	131±35	102±32	-22%	<0.05

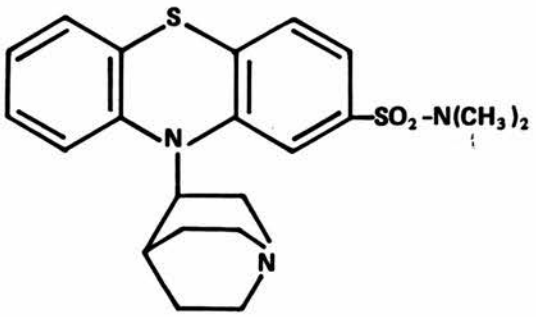
Table 5.1 III **Inhibition of nocturnal acid and pepsin**

	Acid Output (mmol ± SEM)				Pepsin Output (mg ± SEM)			
	Control	Drug	Change	p	Control	Drug	Change	p
Trimipramine	36.4±8.4	42.0±6.7	+16%	ns	541±94	583±47	+ 8%	ns
Mianserin	40.5±5.2	25.6±3.3	-37%	<0.01	640±70	368±52	-43%	<0.05
Quisultidine								
100mg	55.3±7.8	39.6±9.3	-28%	<0.05	703±74	624±121	-11%	ns
200mg	100.2±18.3	30.3±10.5	-70%	<0.01	752±95	380±107	-49%	<0.01
300mg	50.5±7.9	11.0±4.1	-78%	<0.01	785±117	220±83	-72%	<0.01

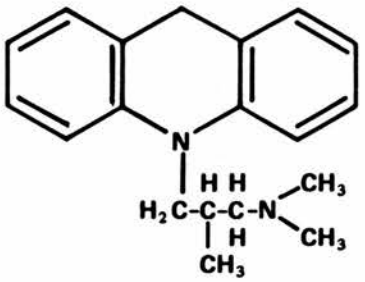
Fig 5.1 I Structure of mianserin, trimipramine and quisultidine



MIANSERIN



LM 24056



TRIMIPRAMINE

5.2 Pirenzepine

5.2.1 Pharmacology

Pirenzepine is an antimuscarinic compound which, in adequate dosage, accelerates the healing rate of duodenal ulcers in man. Combined four and six week healing rates with 100mg and 150mg are 67% and 76% respectively, but the corresponding rate for doses of less than 100mg is 58%, suggesting a dose-response relationship. After one year of maintenance therapy approximately 70% of ulcers remain in remission. These results are not significantly different from those achieved with H2 receptor antagonists. The incidence of side effects also appears to be dose-related - at doses of 100mg and 150mg daily, 14% of patients admitted to dry mouth. The combination of pirenzepine and cimetidine has potent anti-secretory and ulcer-healing effects. The most effective roles for this compound are in healing refractory ulcers (in combination with an H2 receptor antagonist) and in maintaining ulcer remission.

The polycyclic compound pirenzepine is a pyrido-benzodiazepine (Fig 5.2 I) which has a selective anti-muscarinic action since it exerts gastric anti-secretory effects (M1) in doses which cause relatively little or no effect at other cholinergic receptor sites (M2) such as small bowel, bladder, salivary glands and pupils. In vitro studies have confirmed muscarinic receptor sites with high (M1), medium and low (M2) affinity for binding with pirenzepine (130,153) and the dissociation constant differs by a factor of 40. Although in addition to the peripheral sympathetic ganglia, M1 receptors may be found in the central nervous system, central effects of pirenzepine are reduced by the hydrophilic nature of the drug, causing minimal transfer across the blood-brain barrier - levels of drug within the cerebrospinal fluid are only 10% of those in plasma (194). Bioavailability of the drug, normally

20-30%, is reduced by around 10% when ingested with food (152).

5.2.2 Secretory Studies

Pirenzepine is a competitive antagonist of acetyl choline and, as expected, will inhibit vagally stimulated gastric secretion (eg by modified sham feeding) to a greater extent than direct stimulation by secretagogues such as histamine or pentagastrin, or other exogenous muscarinic agonists (369,213,108,127). The primary effect on acid output is on volume rather than on acid concentration (36,125,219,340), although two studies (311,195) demonstrated a reduction in concentration to almost as great an extent as volume. Howden et al (174) examined the effect of nocturnal administration of pirenzepine 100mg or 150mg on gastric secretion. Both volume and acid concentration were significantly inhibited by approximately 50%, although the degree of inhibition exerted by the two doses was not significantly different. With a single nocturnal dose of pirenzepine 50mg in duodenal ulcer patients Corinaldesi (78) also demonstrated that volume and acid concentration are significantly depressed, although to a lesser degree in view of the lower dose.

Londong et al (239) examined the effect of cimetidine, pirenzepine or a combination of the two drugs on peptone-stimulated acid secretion. Cimetidine alone inhibited acid (mmol/3hrs) from 56.6$\pm$8.4 to 22.9$\pm$4.3 (60%) and pirenzepine alone to 24.0$\pm$5.1 (58%). In combination, however, acid secretion was further suppressed to 6.0$\pm$1.1 (89%) suggesting a synergistic effect. Deakin et al (90) also showed a synergistic effect on gastric acid inhibition by combining pirenzepine and cimetidine.

5.2.3 Duodenal Ulcer Healing

A review of the literature on endoscopically controlled, double-blind trials of pirenzepine in duodenal ulcer reveals a total of thirty studies - sixteen placebo-controlled (three of which also with a cimetidine limb) and fourteen cimetidine-controlled (69,14,128, 94,270,104,361,95,286,170,134,93,392,62,131,166,197,13,148,36 5,383,289, 110,82,38,273,30,233,38,109,266). The 50mg and 75mg pirenzepine groups have been combined (three of these studies commenced with one week of 75mg daily then reduced to 50mg daily) with a four week healing rate of 58% (Table 5.2 I). This rate was increased to 68% and 77% with 100mg and 150mg pirenzepine respectively. After four weeks, the healing rate with cimetidine 1g daily was 73% and the placebo rate was 40%. These findings are summarised in Table 5.2 II and depicted graphically in Fig 5.2 II. In only one trial was placebo as effective as pirenzepine (270), but an eight week healing rate of 80% with placebo was achieved in this study and no difference between this group and those treated with cimetidine (86% healing) could be shown. It may well be that healing rate improves with time as well as dose, but the available data (14/17 with 100mg) are not sufficient to support this concept.

5.2.4

Duodenal Ulcer Maintenance Treatment

459 patients with a healed duodenal ulcer have been randomised in 9 trials to either pirenzepine (30-100mg/day), cimetidine 400mg, no therapy (70), and placebo (104,299,66,187,15,83,276,274). Although a trend towards lower relapse rates has been established with the lower doses, a statistically significant difference from placebo has only

been established using 100mg/day or more. Using 150mg daily Morelli et al (274) demonstrated a significant difference in relapse rates from a placebo- treated group when treatment was administered for two six-week periods annually, from March-April and September-October over two years suggesting that seasonal prophylactic therapy is efficacious. Although the total numbers entered into maintenance trials might, at first sight, suggest that fairly powerful predictions could be made concerning relapse rates, the numbers are considerably reduced since many of the studies only reported on the relapse rate at six months. The relapse rate for those studies extending to one year was 82% on placebo, 38% on pirenzepine (30mg, 50mg and 100mg) and 33% on cimetidine (Table 5.2 III).

5.2.5 Refractory Ulcer

Dal Monte et al (84) identified patients who had proved unresponsive to treatment with pirenzepine 150mg/day and cimetidine 1g/day for two months each. Seventy five patients were randomised to three groups. After six months 85% of those receiving combined therapy of pirenzepine 75mg and cimetidine 400mg daily had healed, as compared with 35% of those continuing on cimetidine 1g/day and 41% of those receiving pirenzepine 150mg/day ($p < 0.01$). Two studies (90,69) demonstrating synergistic anti-secretory activity of the two drugs therefore are particularly relevant within this context.

5.2.6 Side Effects

With a dose of pirenzepine 75mg daily, no change in the intraocular pressure in a group of patients with open- and closed-angle glaucoma was

recorded (349,375) and no change was recorded in residual volume or bladder emptying in a group of patients with prostatic hypertrophy (140). Salivary secretion was reduced by 26%, however, in a group of healthy subjects taking pirenzepine 100mg daily (196) - this figure was even higher in an unpublished, single-dose tolerance study at McMaster University in Canada, performed in 30 normal volunteers (141). Placebo or pirenzepine 50mg, 100mg and 150mg were given in double-blind fashion and dry mouth was confirmed on direct questionning by 17%, 33%, 60% and 67% respectively.

In the short term studies pirenzepine was well tolerated by most patients and, in a post marketing surveillance (137) only approximately 2% were withdrawn from therapy. Dry mouth was the most common side effect, with 14% of those taking 100 or 150mg daily affected. Blurring of vision was less common - 1.1% with 100mg but increased to 5.6% with 150mg daily. Other side effects such as diarrhoea, constipation and headache were no more common at the higher dose.

5.3 **Discussion**

All of the mechanism by which the various polcyclic drugs influence gastric secretion have not been defined. However, the dissimilar patterns of altered gastric secretion after dosing indicate that the mechanisms of the peripheral (gastric) effects of these drugs differ, as do their central actions, and this may be attributed, at least in part, to interactions with different cellular receptors (153).

Anticholinergic drugs inhibit gastric secretion (194) and, as both trimipramine and quisultidine produce dryness of the mouth when given in high dosage (268,50), it has been suggested that polycyclic drugs affect

gastric secretion by blocking muscarinic receptors. However, mianserin is reported not to exert anticholinergic effects in man (60) and, although quisultidine has also been stated to exert virtually no anticholinergic effects, its metabolites do show affinity for muscarinic receptors (271).

Mianserin exerts potent anti-serotonergic effects in peripheral tissues (255) but has no effect on serotonin-induced contraction of isolated rat gastric fundus (122) and, in any case, the effects of serotonin on gastric secretion in man are inhibitory (192).

Several antidepressant drugs, including mianserin and imipramine, are considered to interact with histamine H2 receptors (255) and to exert an inhibitory effect on histamine-sensitive adenyl cyclase in mammalian brain (202), although it has also been shown that in vivo the cerebral H2 receptor antagonism is not significant (284). Histamine H2 receptors are important in regulating gastric secretion (355) and one must therefore consider the possibility that some of the gastric anti-secretory effects of polycyclic drugs are attributable to H2 receptor blockade. However, against this hypothesis is the finding that quisultidine does not inhibit histmaine-stimulated gastric secretion (271), while trimipramine actually augments histamine-stimulated secretion in man (43), just as nocturnal secretion has been augmented by trimipramine in the present study.

The action of pirenzepine has been more clearly defined, and is discussed in the section on pharmacology in 5.2.1. In addition to the selective anti-muscarinic effect, however, it has also been shown that pirenzepine, quisultidine, mianserin and trimipramine all inhibit calmodulin activity (265). Since the transport of calcium is involved in gastric secretory processes (331), it may be that the polycyclic drugs

affect gastric secretion by inhibiting the movement of calcium, which is necessary for the secretory processes of the gastric parietal and chief cells.

In conclusion, it seems likely that the differences in gastric actions reflect different peripheral (and perhaps also central) actions and mechanisms. These drugs are all of real, or potential, benefit in the treatment of ulcer disease and may provide more insight into the mechanisms of accelerated ulcer healing.

Table 5.2 I

Duodenal Ulcer Healing Data
Pirenzepine vs Placebo/Cimetidine

		PZP		CMT		Placebo	F/U
Study	No.	Dose mg	Heal %	Dose g	Heal %	Heal %	wks
Cerlek	34	50	11/15 (73)			8/19 (42)	4
Barbara a)	79	75+50	23/44 (52)			12/35 (34)	4
Gasbarrini	21	75+50	9/12 (75)			4/9 (44)	4
Dobrilla a)	26	75+50	5/11 (45)			8/15 (53)	4
Mittelstaedt	28	50	13/14 (92)	1	14/14 (100)		4
Eichenberger	65	75	11/22 (50)	1	16/22 (73)	12/21 (57)	4
	(61	75	13/19 (68)	1	19/22 (86)	16/20 (80)	8)
Sonnenberg	134	75	25/45 (55)	1	34/44 (77)	25/45 (55)	4
Dobrilla b)	30	75	5/13 (38)	1	10/17 (59)		4
Oselladore a)	30	75	9/15 (60)			6/15 (40)	4
	417		**111/191(58)**				
Barbara a)	92	100	32/46 (70)			15/46 (32)	4
Hoffenberg	50	150+100	12/25 (48)			10/25 (40)	4
Gibinski	121	100	45/58 (78)			32/63 (51)	4
Brunner	254	100	81/126(64)	1	94/128(73)		4
Giacosa	60	100	24/30 (80)	1	25/30 (83)		4
Henry	50	100	14/24 (64)	1	17/26 (26)		4
Jaup	75	100	27/37 (73)	0.8	29/38 (76)		4
Ayoola	36	100	13/17 (77)	1	15/19 (79)		4
			(14/17 (82)	1	17/19 (90)		8)
Guslandi	84	100	30/42 (72)	1	25/42 (60)		4
	822		**278/405(68)**				
Do	38	100	14/18 (78)			7/20 (35)	6
Vollenweider	33	100	14/18 (78)			8/15 (54)	6
Sternini	39	100	15/19 (79)	1	17/20 (85)		6
Trotman	115	100	39/53 (74)	1	52/62 (84)		6
Paoluzi	96	100	15/46 (33)	1	28/50 (56)		6
Fakunle	30	100	11/15 (73)	1	10/15 (67)		6
	351		**108/169(64)**				
Oselladore a)	30	150	13/15 (87)			6/15 (40)	4
D´Imperio	20	150	9/10 (90)			5/10 (50)	4
Benvestito	20	150	8/10 (80)			3/10 (30)	4
Laugier	100	150	31/50 (62)			15/50 (30)	4
Evreux	65	150	30/33 (91)	1	22/32 (69)		4
	235		**91/118(77)**				
Bianchi Porro	85	150	21/29 (72)	1	21/28 (75)	10/28 (36)	6
Morelli	29	150	11/14 (79)			2/15 (13)	6
Meunier	64	150	25/33 (76)	1.2	22/31 (71)		6
	178		**57/76 (75)**				

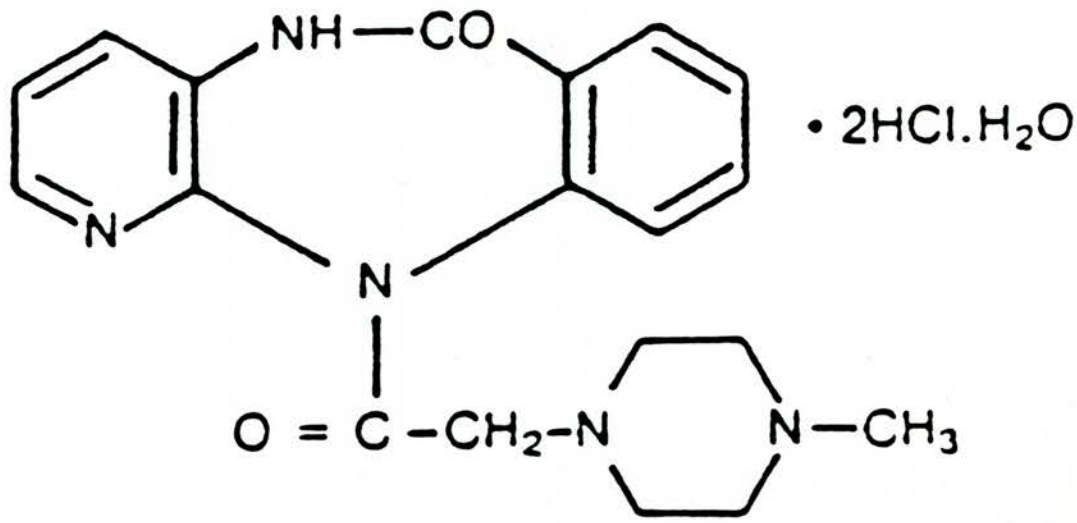
Table 5.2 II **Summary of Ulcer Healing Data**
Pirenzepine vs Placebo/Cimetidine

	PZP			CMT			Placebo		F/U
No. of Studies	Dose	Heal	%	Dose	Heal	%	Heal	%	wks
9	75+50	111/191	(58)						4
9	100	278/405	(68)	1000	301/412	(73)	161/398	(40)	4
6	100	108/169	(64)	1000	150/206	(73)	27/78	(35)	6
1	100	14/17	(82)						8
5	150	91/118	(77)						4
3	150	57/76	(75)						6

Table 5.2 III **Relapse on Maintenance therapy with**
Pirenzepine, Cimetidine or Placebo

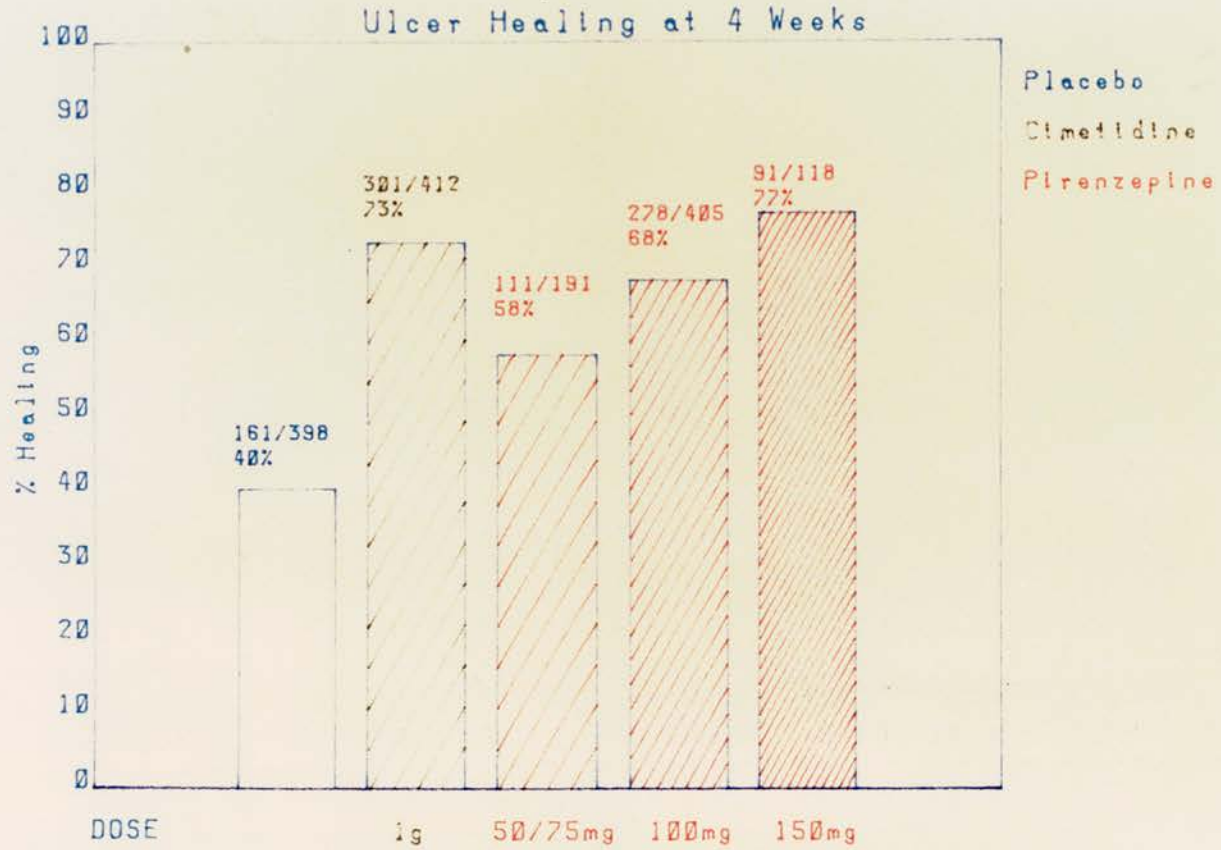
		PZP			CMT			Placebo		
Study	No.	dose	relapse	%	dose	relapse	%	relapse	%	F/U wks
Eichenberger	32	30	4/9	44	400	6/11	55	8/12	67	52
Petrillo	28	50	7/15	47				9/13	69	52
Capria	60	50	5/20	25	400	4/20	20	13/20	65	26
Ireland	89	50	9/43	21	400	8/46	17			52
Cheli	32	50	3/16	19				10/16	63	26
Barberani	30	50	3/15	20				4/15	27	26
Dal Monte	54	100	15/26	58				27/28	96	52
Moshal	52	100	10/16	63	400	11/18	61	14/18	78	52
Morelli	68	150	12/35	34	for 2 6wk periods			25/33	76	32
			11/51	**22**		**4/20**	**20**	**27/51**	**53**	**26**
			45/106	**38**		**25/75**	**33**	**58/71**	**82**	**52**

Fig 5.2 I Molecular structure of pirenzepine



Pirenzepine

Fig 5.2. II Summary of ulcer healing



6 H2 RECEPTOR ANTAGONISTS

6.1 Histamine and Gastric Secretion

6.1.1 Introduction

The aim of this study was primarily to compare levels of histamine, histidine decarboxylase, and histamine methyl transferase in gastric fundic mucosal biopsies in patients with active duodenal ulcer disease and non-ulcer dyspepsia, in order to assess histamine synthesis and degradation in ulcer disease. In addition, I examined the effect of cimetidine 1g/day and ranitidine 300mg/day for four weeks on these three indices of histamine metabolism.

6.1.2 Patients and Methods

Biopsies were taken through an Olympus P2 gastroscope with the standard P2 forceps from the gastric fundus of fasting patients. After weighing, biopsies were homogenised by hand using a ground glass homogeniser in 0.1M phophate buffer at pH 6.5 and 4 degrees C. Using a modification (188) of the radioisotopic method of Snyder and Epps (353), HDC concentration was then calculated in pmol/min/mg protein and concentration of histamine in pmol/min/mg protein obtained from a plotted standard curve. HMT was calculated using a modification (236) of the double isotope technique of Taylor and Snyder (377) and the concentration was expressed in pmol/min/mg protein.

The control population was derived from patients who were undergoing gastroscopy for investigation of upper abdominal pain but in whom the gastroscopy revealed no abnormality. All patients in the study group had an active duodenal ulcer. Table 6.1. I indicates the distribution of age, sex and cigarette consumption in both groups.

The following exclusion criteria were used:

1. Consumption of ulcer healing drugs within the previous three months
2. Previous gastric surgery
3. Consumption of polycyclic drugs at the time of initial endoscopy
4. Excess alcohol consumption (greater than ten pints beer/week or equivalent)
5. Presence of chronic or debilitating disease
6. Age under 16yrs or over 65yrs
7. Gastrointestinal haemorrhage within the previous three months

Statistical analysis was undertaken with the Wilcoxon ranked sum test, in view of the non-parametric nature of the data.

6.1.3 Results

The results are displayed in tabular form in Tables 6.1 II to IV. There is no significant difference between the histamine concentrations of the two combined ulcer groups and the control population. The activity of HDC is unchanged by therapy with H2 receptor blockade, but the concentration of histamine is increased in both treatment groups, to a significant degree ($p < 0.01$) in the ranitidine group. Although the decrease in HMT activity following four weeks of ranitidine therapy is statistically significant ($p < 0.01$) there is also a significant difference ($p < 0.05$) between the pre-treatment activities of HMT in the two ulcer groups.

Table 6.1. I **Demographic profile of control and study groups**

	Number	Age (Mean ± SD)	Sex	Smoker
Control	18	44 ± 11	10M	6
Cimetidine	9	46 ± 15	7M	5
Ranitidine	9	44 ± 16	6M	7

Table 6.1. II **Histamine Concentrations (Mean ± SD) in nmol/ml**

	Pre	Post
Control	17.6 ± 6.3	
Cimetidine	20.1 ± 7.3	28.4 ± 12.9
Ranitidine	19.0 ± 6.1	23.4 ± 9.0
Cimetidine and Ranitidine	19.8 ± 6.5	

Table 6.1 III **HDC Activity (Mean ± SD) in pmol/min/mg protein**

	Pre	Post
Control	3.2 ± 3.8	
Cimetidine	2.7 ± 1.9	2.0 ± 1.7
Ranitidine	2.6 ± 4.0	1.9 ± 1.6
Cimetidine and Ranitidine	2.6 ± 3.1	

Table 6.1 IV **HMT Activity (Mean ± SD) in pmol/min/mg protein**

	Pre	Post
Control	15.9 ± 9.4	
Cimetidine	11.2 ± 12.9	11.6 ± 14.6
Ranitidine	22.4 ± 13.0	11.5 ± 7.9
Cimetidine and Ranitidine	17.1 ± 13.8	

6.2 CM 57755

6.2.1 Introduction and Pharmacology

CM 57755 is a new, furan-based histamine H2 receptor antagonist which was recently reported to be as potent as cimetidine in inhibiting dimaprit-stimulated gastric secretion in cats, but to exert a more sustained gastric inhibitory effect (235). In view of this, and the apparent absence of any effect by this compound on the cytochrome P450 system (300), this study was designed to examine the effect of CM 57755 on nocturnal output and diurnal profile of acid and pepsin concentration, and compare these values with the response to cimetidine in healthy volunteers.

The molecular structure is shown in Fig 6.2 I and the molecular weight of the compound is 408.35. Unpublished studies have shown that, after oral administration, the drug is slowly absorbed with a bimodal absorption profile. The first peak occurs at 1 hour and the second peak (Cmax) at 3 hours after intake. As the second peak is higher than the first, enterohepatic recirculation is unlikely to be an important feature with this compound, as it is with ranitidine and cimetidine. The elimination half life is 2 hrs, and urinary excretion of the parent drug is approximately 50% following oral administration. As total plasma clearance is 47 l/hr and renal clearance is 16-20 l/hr, extrarenal (hepatic) clearance is clearly important.

6.2.2 Subjects and Modifications to Method

Demographic data

Mean	Range	
27	18-32	yrs.
78	64-89	kg

Identical capsules, containing 600mg CM 57755, 600mg cimetidine or placebo were administered under supervision at 1800hrs with a standardised light evening meal.

6.2.3 Results

Overnight secretion of acid was reduced from a median value of 75.4mmol to 25.4mmol by CM 57755 and to 22.9mmol by cimetidine (Table 6.2. I). The decrease from placebo values was highly significant ($p<0.01$) and the inhibitory effect similar with both drugs. When acid output was compared with placebo on an hourly basis the degree of inhibition was significant except for the first hour and the last three hours (Fig. 6.2. II).

The concentration of acid was more than halved ($p<0.01$) throughout most of the night with both drugs, except for the first hour and the last two hours, but did not differ from placebo at any time during the day (Fig. 6.2 III). The differences in acid concentration were reflected by similar increases in pH after administration of both drugs. However, more than two consecutive pH values greater than 4.0 were observed in only two of the ten subjects after cimetidine and in one of these two individuals after CM 57755.

Neither nocturnal secretion of pepsin nor median peptic activity were significantly influenced by cimetidine or CM 57755 (Table 6.2 II and Figs. 6.2 IV and V). Total volume secreted was diminished by approximately 40% with both drugs, although median hourly volume was initially close to placebo values with CM 57755 (Table 6.2 III and Fig. 6.2 VI).

Table 6.2 I **Nocturnal acid output (mmol/12hrs)**

Subject	Placebo	Cimetidine	CM 57755
1	68.6	18.6	17.7
2	24.3	23.0	19.6
3	119.3	90.9	80.9
4	99.6	16.9	28.8
5	108.0	82.8	94.8
6	27.5	22.8	21.6
7	45.1	4.6	5.7
8	82.2	24.9	43.2
9	50.7	4.2	35.2
10	102.0	46.6	22.0
Mean ± SD	71.9 ± 33.9	33.6 ± 30.6	37.0 ± 28.9
% change		53%	49%
Median	75.4	22.9	25.4
% change		70%	66%

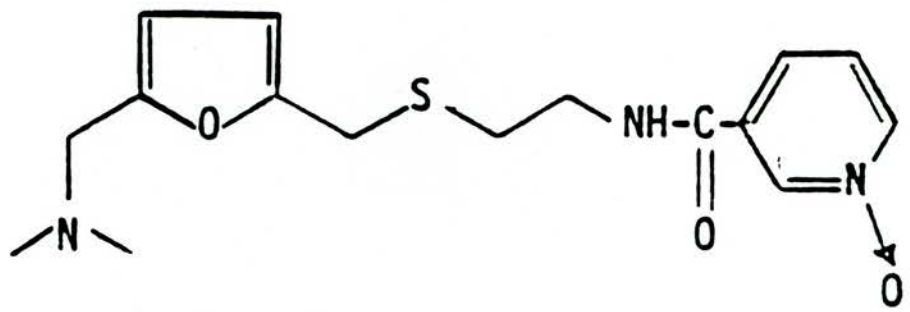
Table 6.2 II **Nocturnal pepsin output (mg)**

1	653	278	417
2	518	841	669
3	1002	1068	1212
4	924	455	720
5	936	1104	1260
6	719	588	756
7	687	168	124
8	668	939	815
9	511	215	895
10	1300	1140	908
Mean ± SD	784 ± 243	680 ± 385	778 ± 338
% change		13%	1%
Median	703	715	786
% change		2%	12%

Table 6.2 III **Nocturnal volume output (mls)**

1	888	360	504
2	456	516	552
3	1068	960	888
4	1056	480	600
5	972	912	1044
6	768	492	564
7	1056	684	564
8	924	684	888
9	526	396	528
10	1020	864	744
Mean ± SD	873 ± 222	593 ± 199	688 ± 190
% change		32%	21%
Median	948	600	582
% change		37%	39%

Fig 6.2 I Molecular structure CM 57755



- CM 57755

$C_{16}H_{21}N_3O_3S$. 2 HCl Mol. Wt. 408.35

Fig 6.2 II Median acid output (mmols)

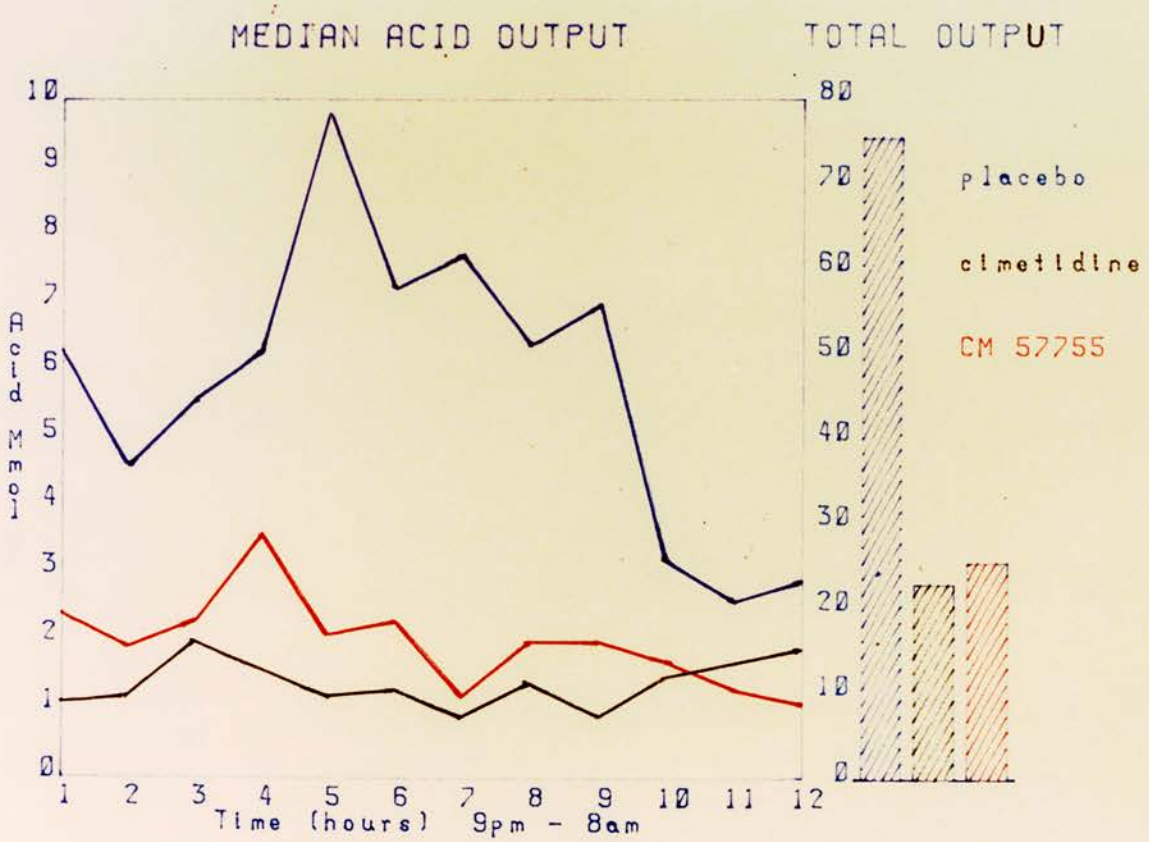


Fig 6.2 III Median acid concentration (mmol/l)

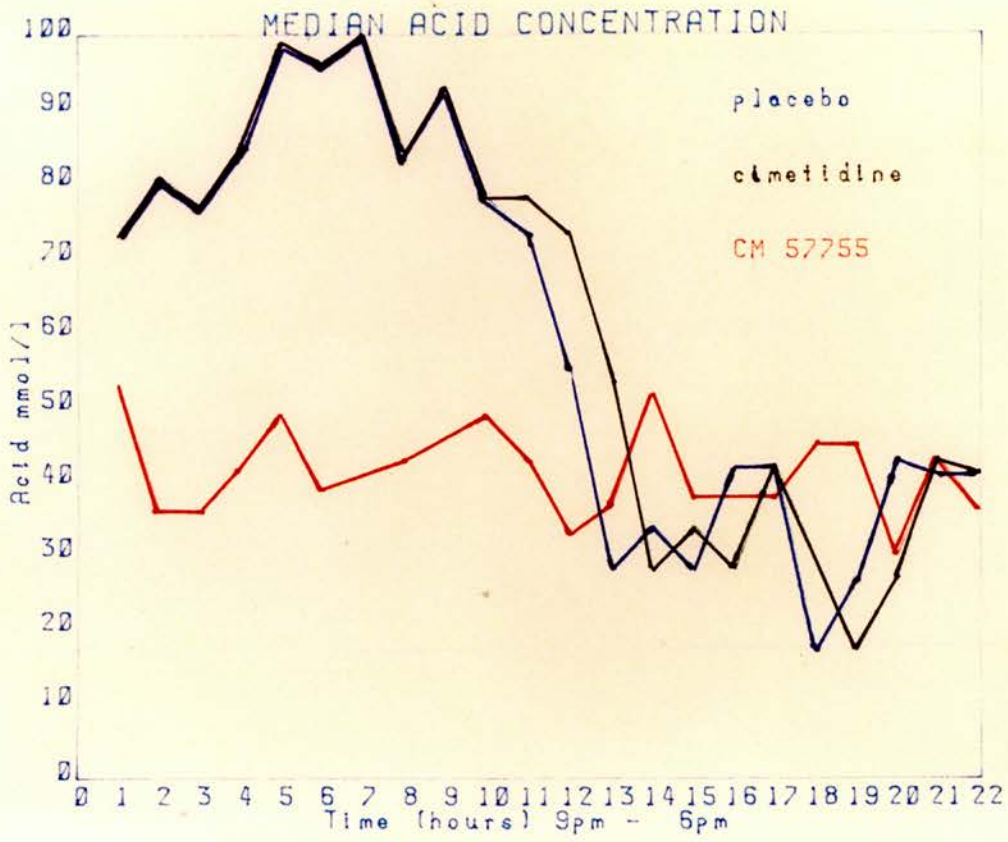


Fig 6.2 IV Median pepsin concentration (mg/l)

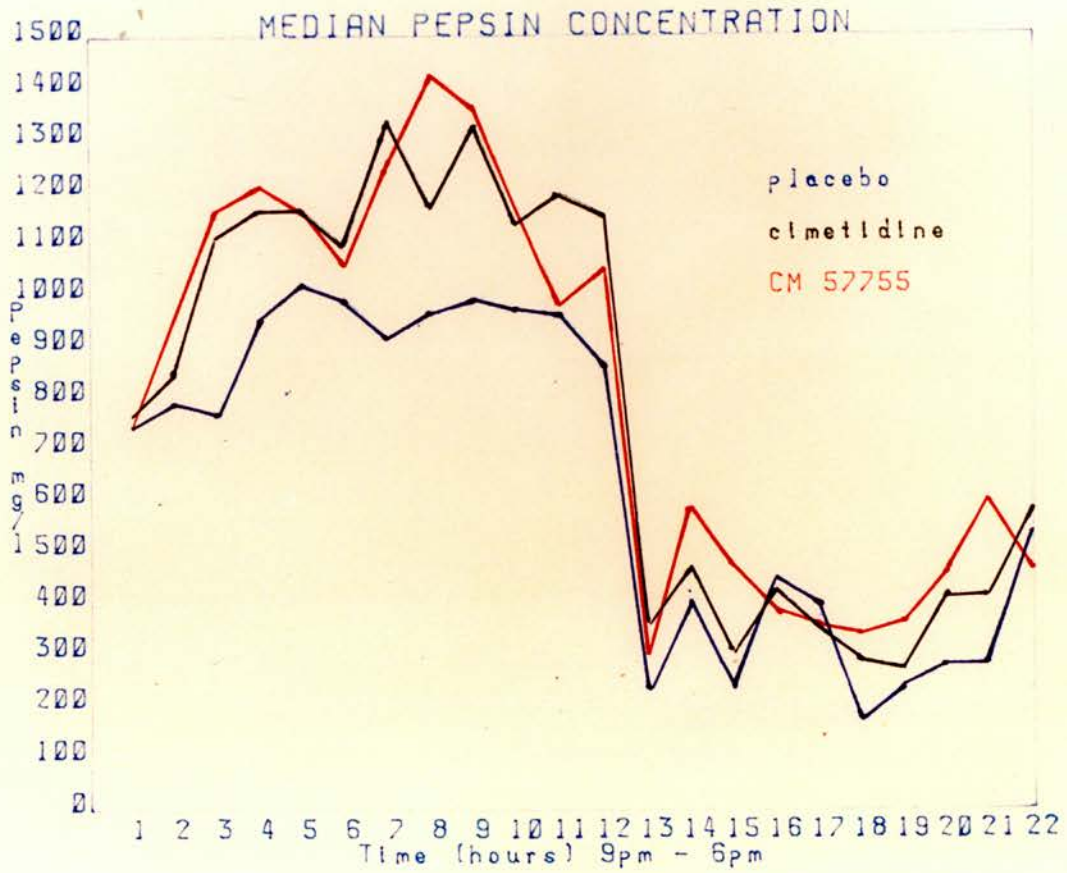


Fig 6.2 V Median pepsin output (mg)

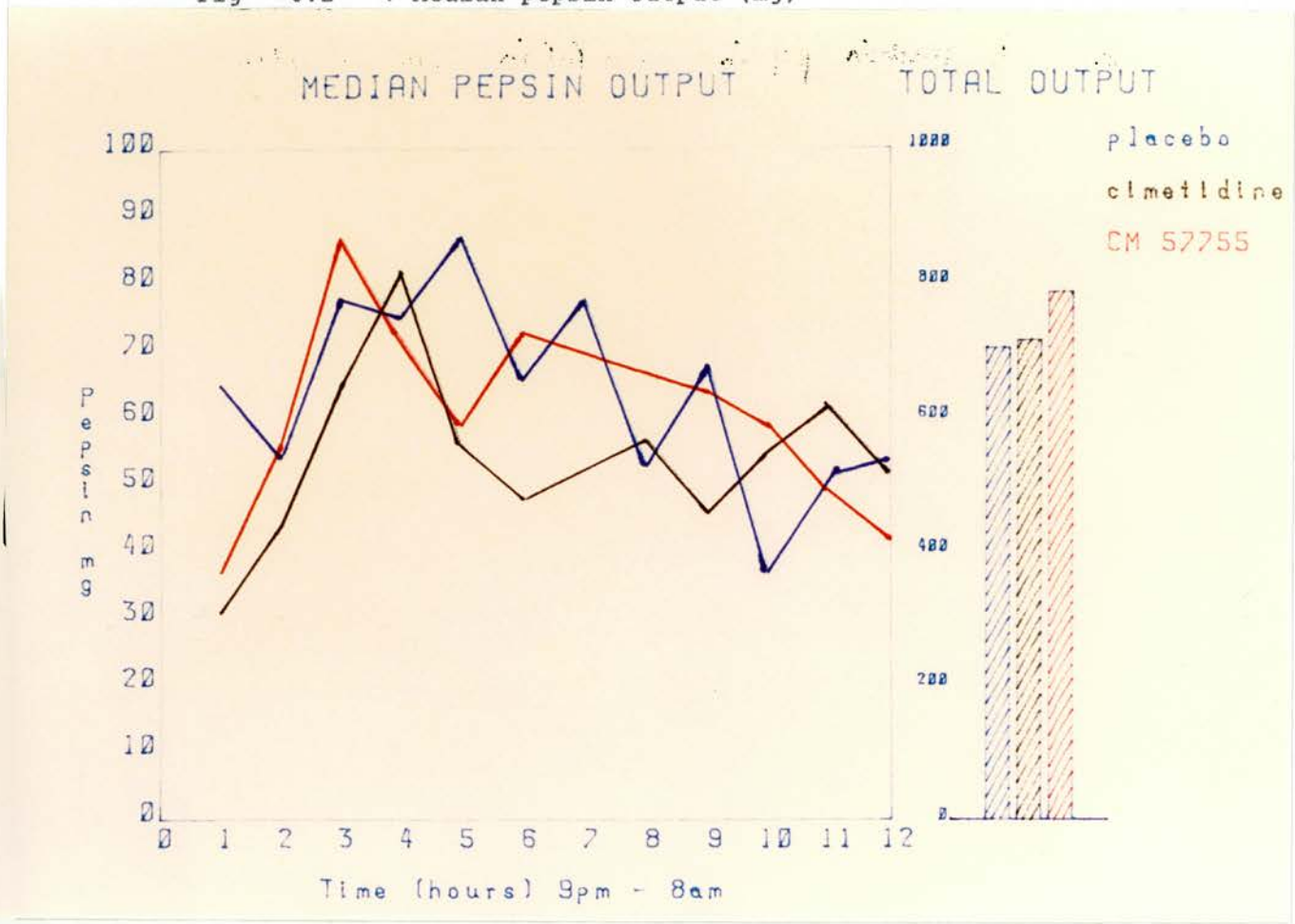
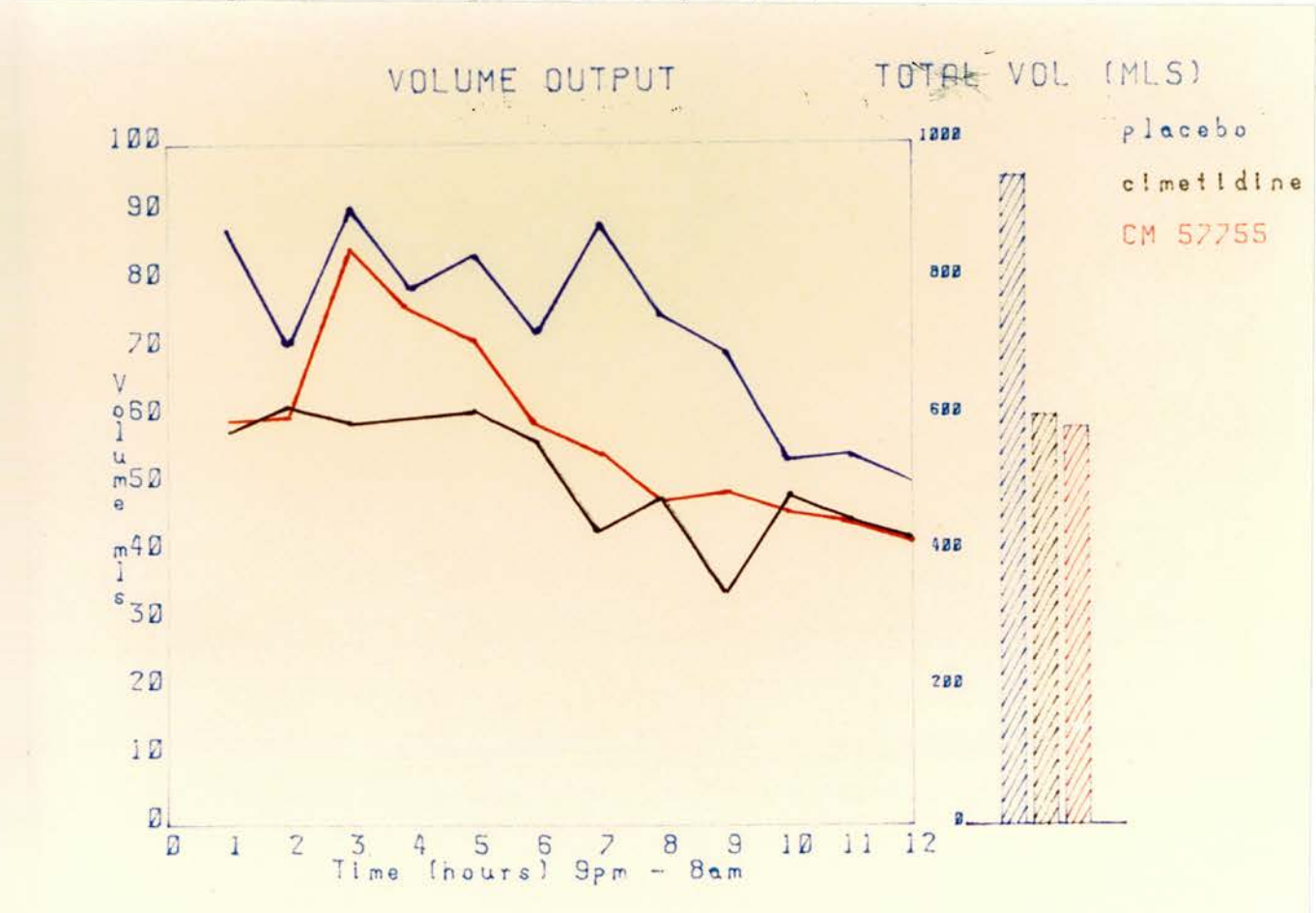


Fig 6.2 VI Median volume output (mls)



6.3 ICI 162,846

6.3.1 Introduction and Pharmacology

ICI 162,846 is a new histamine H2 receptor antagonist of novel structure (Fig 6.3 I). Animal studies have demonstrated a specific, sustained and dose-related action on gastric secretion stimulated by food, histamine and pentagastrin. This sustained action is not dependent on a long plasma elimination half life which, in unpublished studies on the dog, is less than 8 hrs. No effects have been demonstrated on either the androgen receptor or the hepatic microsomal mixed function oxidase system.

Studies were therefore undertaken with four different doses of this drug in ten healthy volunteers in order to characterise the antisecretory properties of the drug in man and to determine optimal dosage for therapeutic trials in patients with peptic ulcer.

6.3.2 Subjects and Modifications to Methods

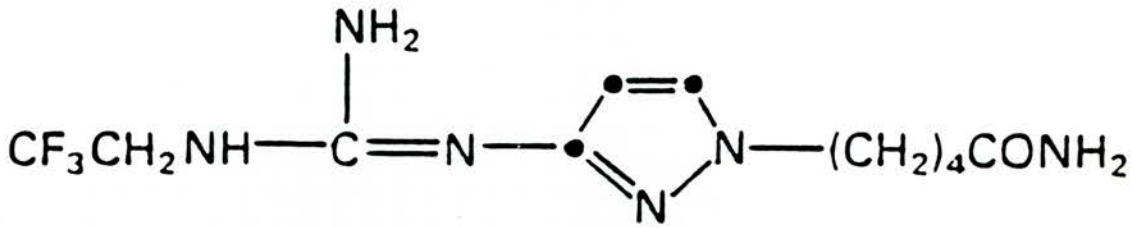
Ten healthy male volunteers aged 21 - 30 with a nocturnal acid output known to be greater than 40mmol/12hrs were studied for five periods of 24hrs, with a minimum of seven days between studies.

Four test doses (0.5, 1.0, 2.5 and 5.0mg) and placebo were each given as a single tablet in randomised double blind fashion at 1800hrs with a standardised light evening meal.

6.3.3 Results

All doses of the test drug were well tolerated and no side effects were encountered. ICI 162,846 produced a dose-related inhibition of nocturnal acid output (Fig 6.3 II). The median reduction in acid output was significant ($p<0.01$) for all doses of the drug and for all time

Fig 6.3 I Molecular structure of ICI 162,846



Structural formula of ICI 162.846.

Fig 6.3 II Acid output (mmol) overnight

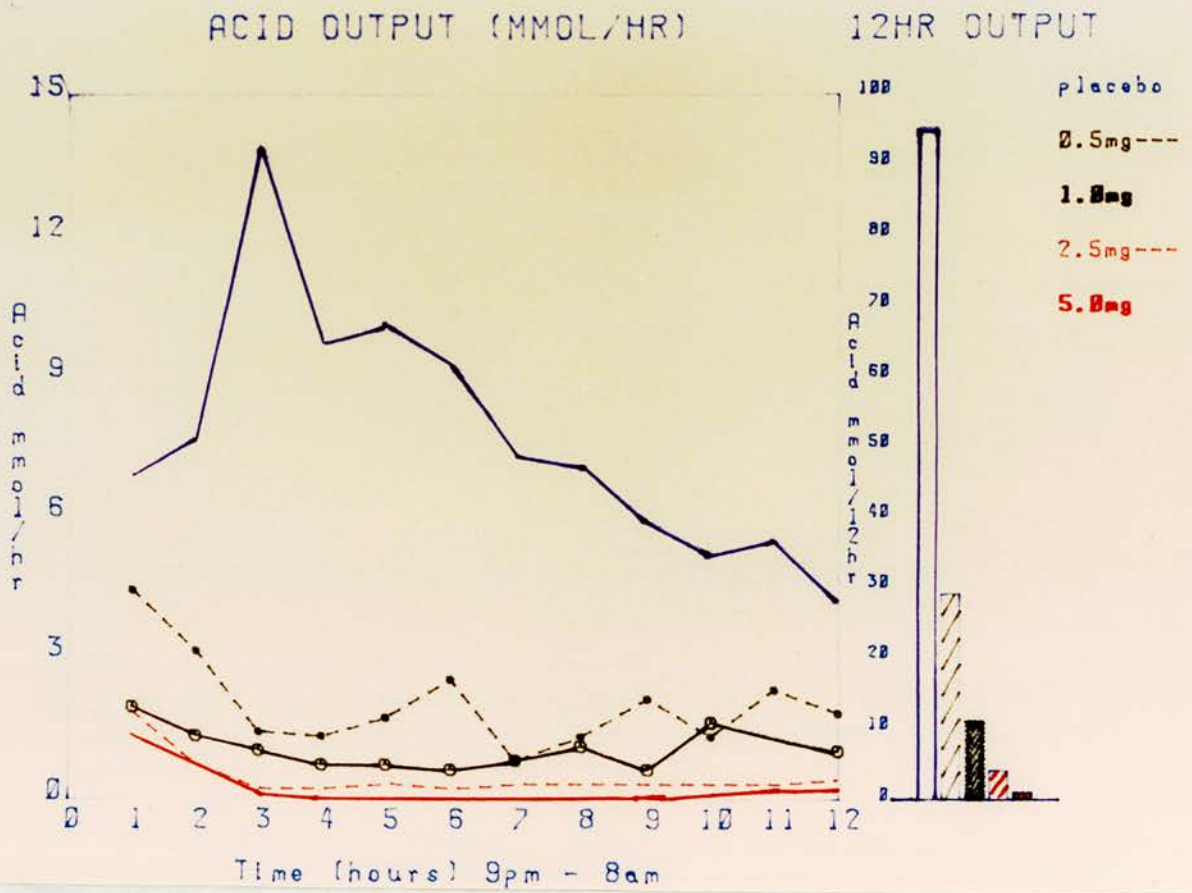


Fig 6.3 III Median acid output as % of placebo

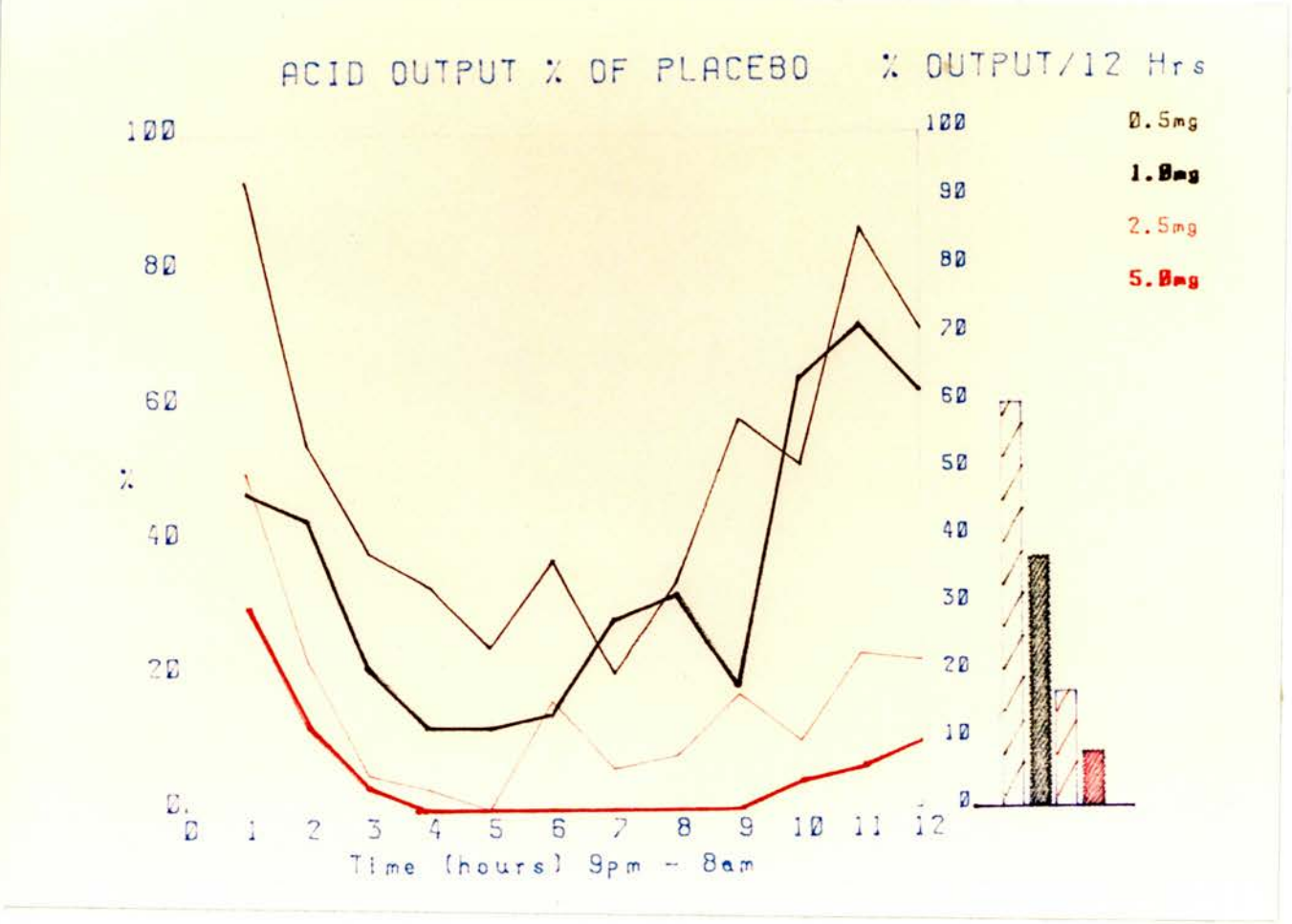


Fig 6.3 IV Median acid concentration (mmol/l)

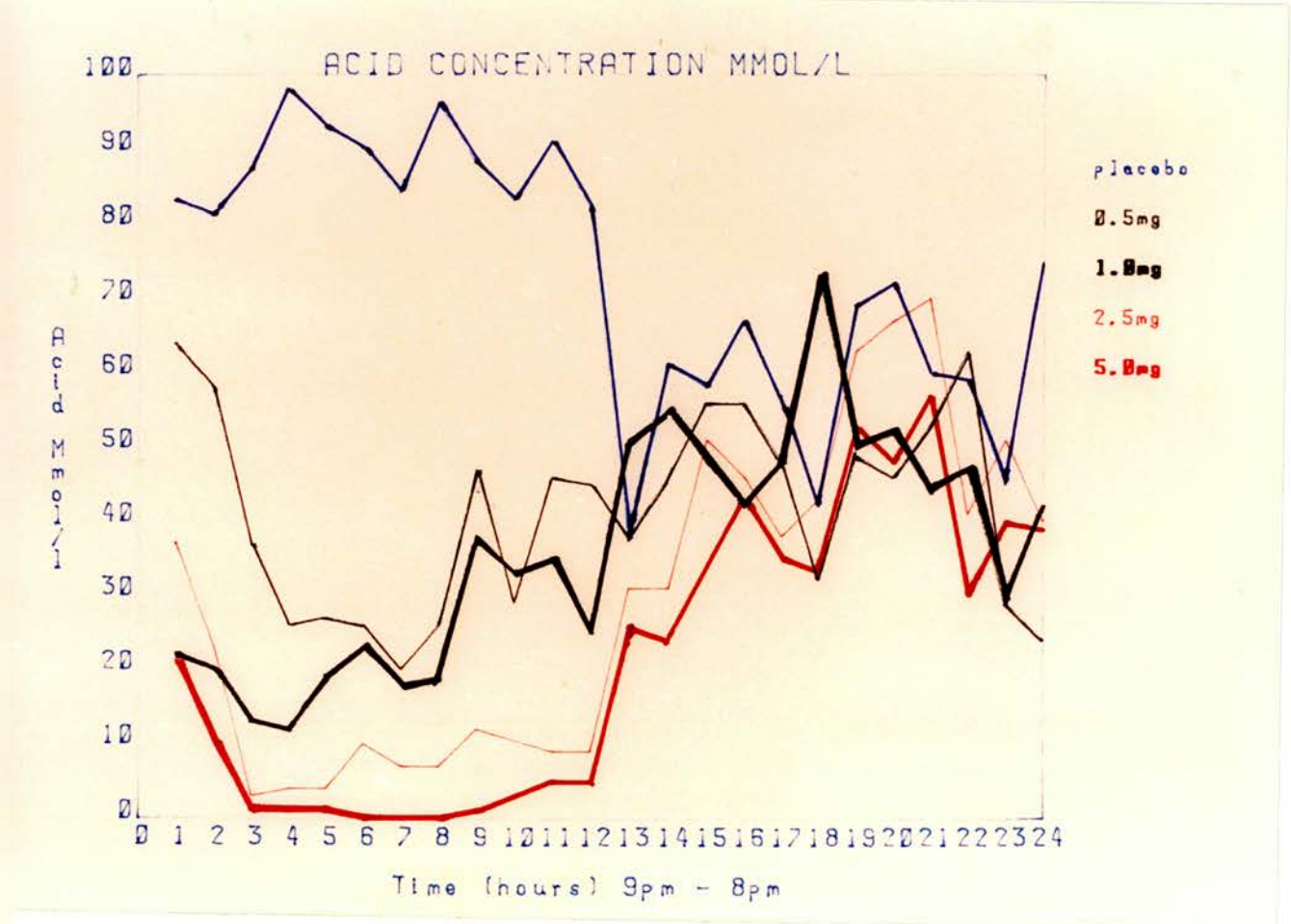


Fig 6.3 V Median pH

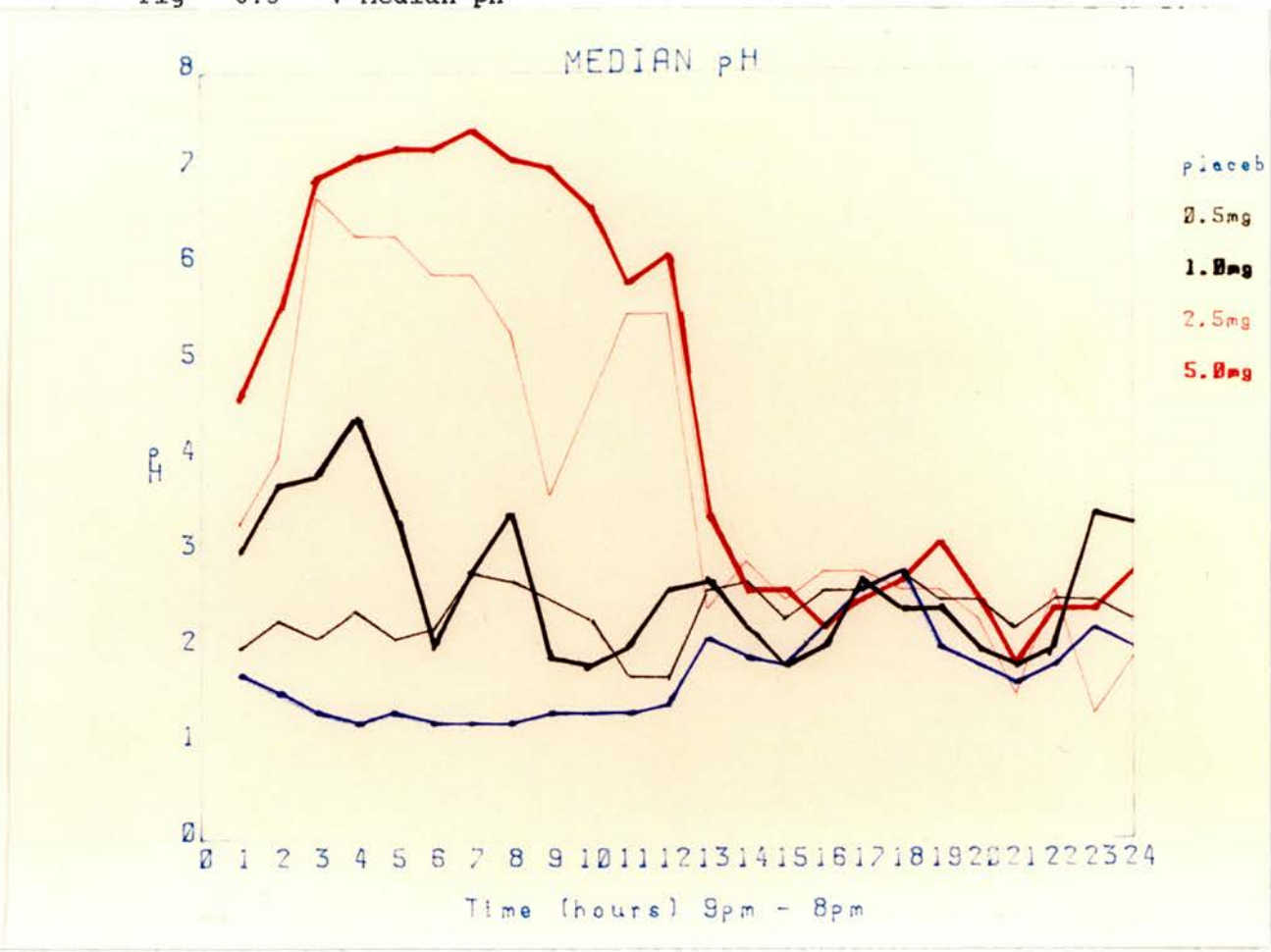
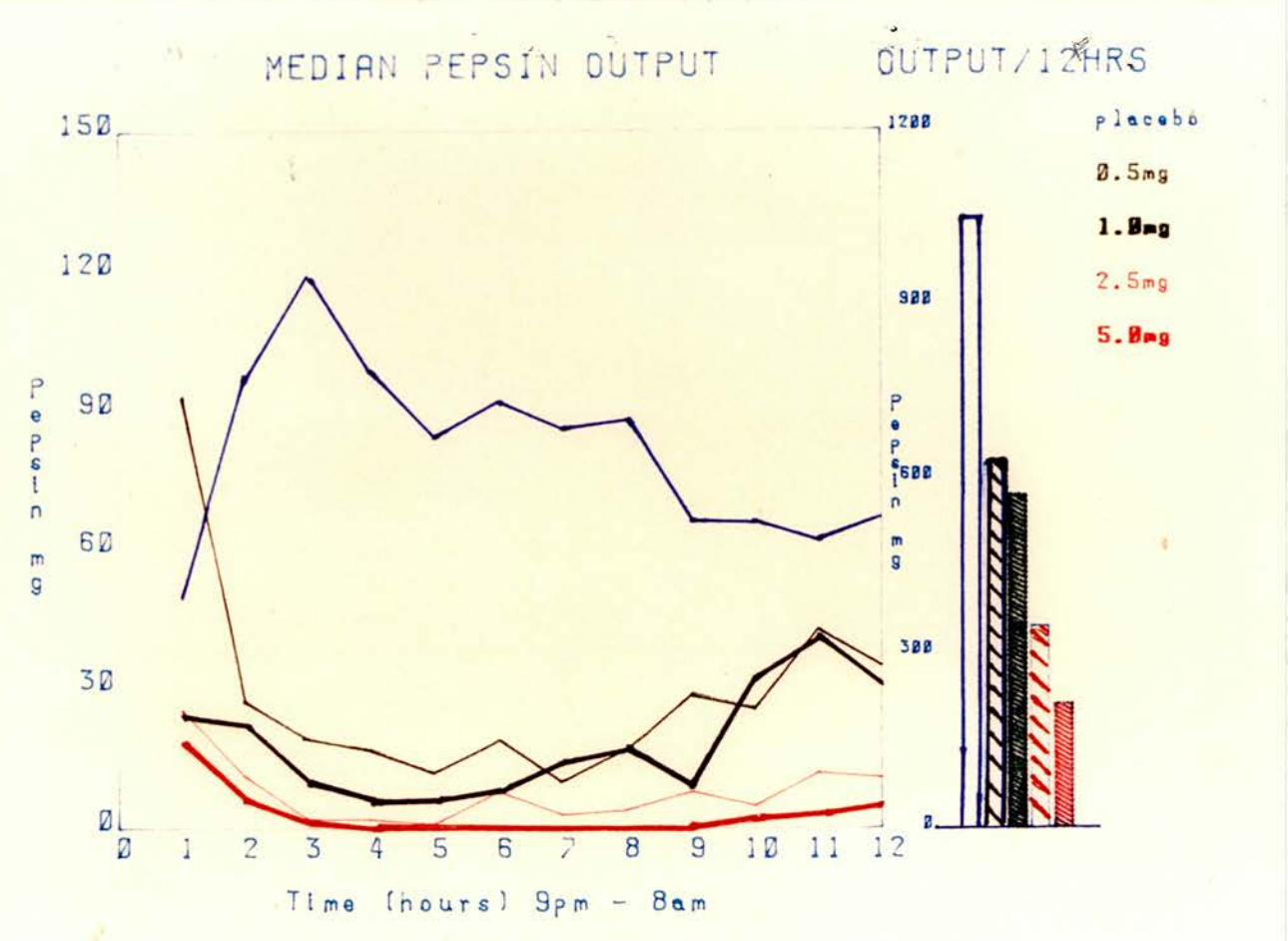


Fig 6.3 VI Median pepsin output



periods between 2000 and 0800hrs except for the first hour and last two hours with the lowest dose (Fig 6.3 III).

The concentration of acid was also reduced in dose-dependent manner until 0800hrs. From 0900hrs until the end of the study none of the values of acid concentration during tests with the different doses of the drug differed significantly from placebo or from each other (Fig 6.3 IV). With the highest dose of the drug the gastric aspirate became virtually anacidic throughout the night, reverting to values not different from placebo by 0900hrs (Fig 6.3 V).

Secretion of pepsin was significantly reduced by all doses of the drug (Fig 6.3 VI), although not as markedly as acid except with the two highest doses, which almost abolished pepsin in seven out of the ten subjects.

6.4 Ranitidine

6.4.1 Introduction and Pharmacology

Ranitidine is a drug which has been extensively tested both in the laboratory, in clinical trials and on the open market (51). In summary, ranitidine is a histamine H2 receptor antagonist with a side chain not dissimilar to that of cimetidine but a furan rather than an imidazole ring (Fig 6.4 I). The bioavailability, calculated from the areaunder the curve from the oral and intravenous doses, is only around 55%, suggesting that there is considerable first pass metabolism of the compound on oral dosing. The mean peak serum concentration of the drug following an oral dose occurs at between 2 and 3 hrs with a concentration at 12 hrs sufficient to give significant inhibition of

acid. The elimination half life is around 3 hrs and renal clearance has been calculated at just over 30 l/h.

The acute healing study was carried from 1978 - 1980, when few reports had been published on the clinical efficacy of ranitidine in peptic ulceration (229,33) and the optimal dose had still to be established. Out patients with peptic ulceration attending British military hospitals have been shown to respond poorly to cimetidine compared with the rest of the population (154) and it was felt that this study would provide a stringent test for the therapeutic efficacy of what was then a fairly new H2 receptor antagonist.

Cumulative recurrence rates for duodenal ulcer range from 16% to 59%, depending on the country and centre from which the results are reported (52). The second study assesses the value of continuing maintenance therapy with ranitidine for longer than one year and also examines the clinical features of the ulcer recurrence in the active and placebo treatment groups.

6.4.2 Ulcer Healing in Service Personnel

6.4.2.1 Patients and Methods

After informed consent, eighty patients presenting to three military hospitals with endoscopically-proven peptic ulcer were entered into the trial. One patient had a gastric ulcer and all other patients either had duodenal or pre-pyloric ulceration. Two patients had previously undergone vagotomy and pyloroplasty, one had rheumatoid arthritis and one had a past history of relapsing pancreatitis. By double blind random allocation patients were given either ranitidine 100mg three times daily or placebo for four weeks, during which time they were permitted access to antacids (stage I). Endoscopy was then

repeated and a further four weeks of ranitidine 100mg three times daily given to those in whom any degree of ulceration peristed.

Following further endoscopy, the randomisation code for stage I was broken and those with persisting ulceration divided into two groups. Those who had already received ranitidine for eight weeks were withdrawn from the trial. Those who had initially received placebo were given a further four weeks (stage II) of ranitidine and re-endoscoped.

Smoking habits, alcohol consumption and the number of unconsumed tablets were recorded at the end of each stage. Any patient drinking more than three pints of beer or two whiskies daily was deemed to be an "above average drinker". Routine haematology and biochemistry were performed on entry and the end of stages I and II.

6.4.2.2 Results

Of the 80 patients who entered the trial, 2 defaulted during stage I, one was withdrawn for non-co-operation and one was withdrawn because his general practitioner discontinued his medication. The remaining 76 patients were available for study.

At the end of stage I, 22 of 37 patients receiving ranitidine were asymptomatic although only 16 (73%) had healed. Of the 15 patients who were symptomatic after four weeks of ranitidine only 4 (27%) had healed. None of the 31 patients who were symptomatic after placebo therapy were healed and 3 (28%) of the 8 who were asymptomatic had healed.

In the placebo group, the ulcer healed in 3 of 39 patients (7.7%). Of 37 patients receiving ranitidine, 20 healed after four weeks of treatment. In the second four weeks of treatment 2 patients defaulted, leaving 15 of whom 5 healed. Of the 36 who failed to heal during

treatment with placebo, 31 completed four weeks of ranitidine and, of these, 25 (81%) were healed. Of the remaining 6 patients, 3 completed a further four weeks of therapy and 2 of these were healed on re-endoscopy. The cumulative healing rates are shown in Table 6.4.2 I.

No significant relationship was demonstrated between healing rates and age, compliance or smoking but a higher proportion of patients in the unhealed groups consumed >3u alcohol daily ($p<0.05$).

One patient whose blood pressure had been recorded as normal at a single reading before entry to the trial was found to have asymptomatic labile hypertension at the end of stage I, during which he received ranitidine. He remained hypertensive at the end of stage II and, although the association with rantidine was strongly doubted, treatment was discontinued. No biochemical or haematological abnormalities were noted which affected clinical management in any way.

Table 6.4.2 I **Cumulative Healing Rates on Ranitidine**

	Stage	Entered	Drop out	Completed	Healed (%)	Cumulative (%)
RNT in stage I	I	39	2	37	20 (54)	(54)
	II	17	2	15	5 (33)	(69)
RNT in stage II	II	36	5	31	25 (81)	(81)
	II	6	3	3	2 (67)	(94)

6.4.3 Ulcer Maintenance

6.4.3.1 Patients and Methods

Endoscopic confirmation, both of initial ulceration and of healing (either with ranitidine 300mg or cimetidine 1g daily) was obtained before entry to the trial. Therapy was then commenced with ranitidine 150mg at night and patients reviewed at 1,2,4,6,9 and 12 months after the start of maintenance treatment, or more frequently if necessary. Repeat endoscopy was performed at 6 and 12 months, or earlier if symptoms recurred. Clinical details of those entering the open maintenance phase of the study are shown in Table 6.4.3 I.

Patients whose ulcers remained healed at the end of 12 months of treatment were asked to take part in a further double-blind study in which they were randomised to continuation of ranitidine 150mg at night or identical placebo. Follow-up was similar to that during the first year of maintenance therapy. Patients were withdrawn from the study if they failed to follow the protocol or if they developed unwanted side effects attributable to drug therapy.

Annual recurrence rates were calculated by life-table analysis, and differrences in recurrence rates were assessed for statistical significance by the log-rank test (298). Fisher's exact test was used to compare intergroup differences in sex distribution, smoking, ulcer complication and frequency of symptomatic and asymptomatic recurrences.

6.4.3.2 Results

Open maintenance study

One hundred and seventy one patients were entered into the study and thirty three patients were withdrawn (Table 6.4.3 II). The cumulative 12-month symptomatic recurrence rate was 15%, with an overall rate of 38% when asymptomatic recurrences were included (Fig 6.4.3 II).

Of the 54 patients whose ulcers recurred during the study, 22 presented with pain and 1 also had a haematemesis. Eighty two patients remained endoscopically healed at the end of the year. Ulcer recurrences were significantly commoner in smokers than in non-smokers (Table 6.4.3 III).

Double-blind study:

Forty seven patients agreed to participate in the study. Twenty one received ranitidine and twenty six received placebo (Table 6.4.3 IV). Two of the patients receiving ranitidine developed symptomatic recurrence and one an asymptomatic recurrence, giving a 12-month cumulative recurrence rate of 18% (Fig 5.4.3 III). Of the patients receiving placebo, 16 developed symptomatic recurrence and 4 developed asymptomatic recurrence, giving 12-month rates of 71% and 87% for symptomatic and total recurrences respectively. Four of the sixteen symptomatic recurrences were associated with haemorrhage.

Pattern of ulcer recurrence:

Fifty seven patients had an ulcer recurrence while receiving ranitidine (54 in the open study and 3 in the double-blind study). Twenty patients had ulcer recurrence after randomisation to placebo. Asymptomatic ulcers were significantly commoner in patients receiving ranitidine. Haemorrhage was significantly commoner in patients receiving placebo (Table 6.4.3 V). Three of the four patients with haemorrhagic ulcer recurrence had presented with haemorrhage before inclusion in the maintenance studies.

While not included in the current analysis, it is worth noting that, of the 31 patients withdrawn from the 2 studies for overt non-compliance or failure to attend for follow-up, 9 were eventually referred again with symptomatic recurrence and 3 with haemorrhage.

Table 6.4.3 I **Clinical details of patients entering open maintenance study**

Age (yrs.) mean ± SEM	44.1 ± 1.0
Male/female	112/59
Smoker/non-smoker	121/50
Median ulcer history years (range)	9 (0-55)
No. with prev. ulcer haemorrhage	30
No. with previous perforation	8

Table 6.4.3 II **Reasons for withdrawal from open maintenance study**

Failure to attend for follow-up	24
Overt non-compliance	7
Drug-related side-effect (diarrhoea)	1
Change of employment precluding follow up	1

Table 6.4.3 III **Comparison of patients in remission and recurrence after 12 months**

	Remission n=82	Symp. Recurrence n=22	Asymp.Recurr. n=32
Age (yrs.) Mean ± SEM	46.2 ± 5.5	43.9 ± 3.0	47.0 ± 1.5
Male/female	50/32	10/12	24/8
Smoker/non-smoker	52/30	18/4	24/8
Median ulcer history	8	8	15
range	0-55	0-30	0-45

Table 6.4.3 IV **Clinical details of patients randomised to ranitidine or placebo**

	Ranitidine n=21	Placebo n=26
Age (mean ± SEM)	48.9 ± 2.2	50.7 ± 2.3
Male/female	11/10	17/9
Smoker/non-smoker	15/6	18/8
Median ulcer history range	10 0-55	11 2-30
Prev. haemorrhage	4	8
Prev. perforation	3	1

Table 6.4.3 V **Details of recurrences in patients receiving ranitidine or placebo**

	Recurrences on ranitidine	Recurrences on placebo
No. of patients	57	20
Symptomatic / Asymptomatic	24/33	16/4 *
Haemorrhage/uncomplicated	1/56	4/16 **

* $p<0.01$

** $p=0.028$

Fig 6.4 I Molecular structure of cimetidine and ranitidine

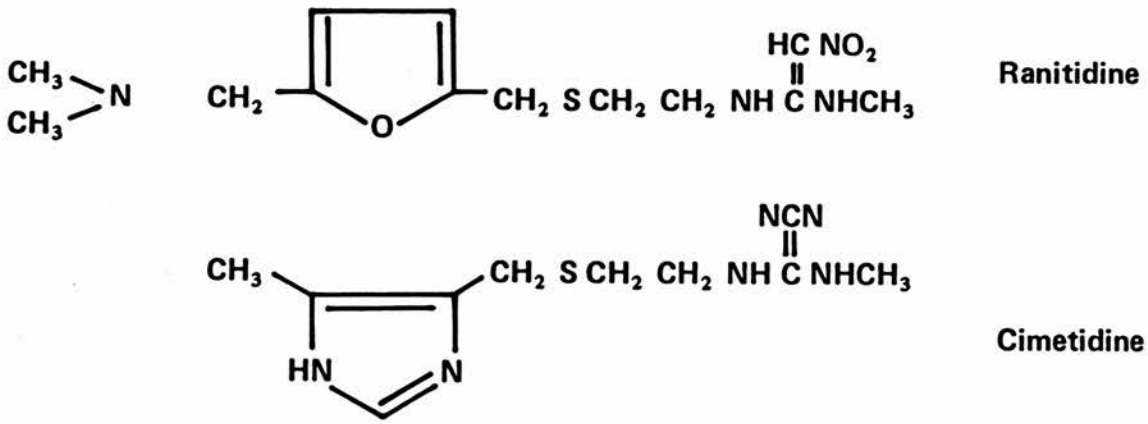


Fig 6.4 II Cumulative remission rates

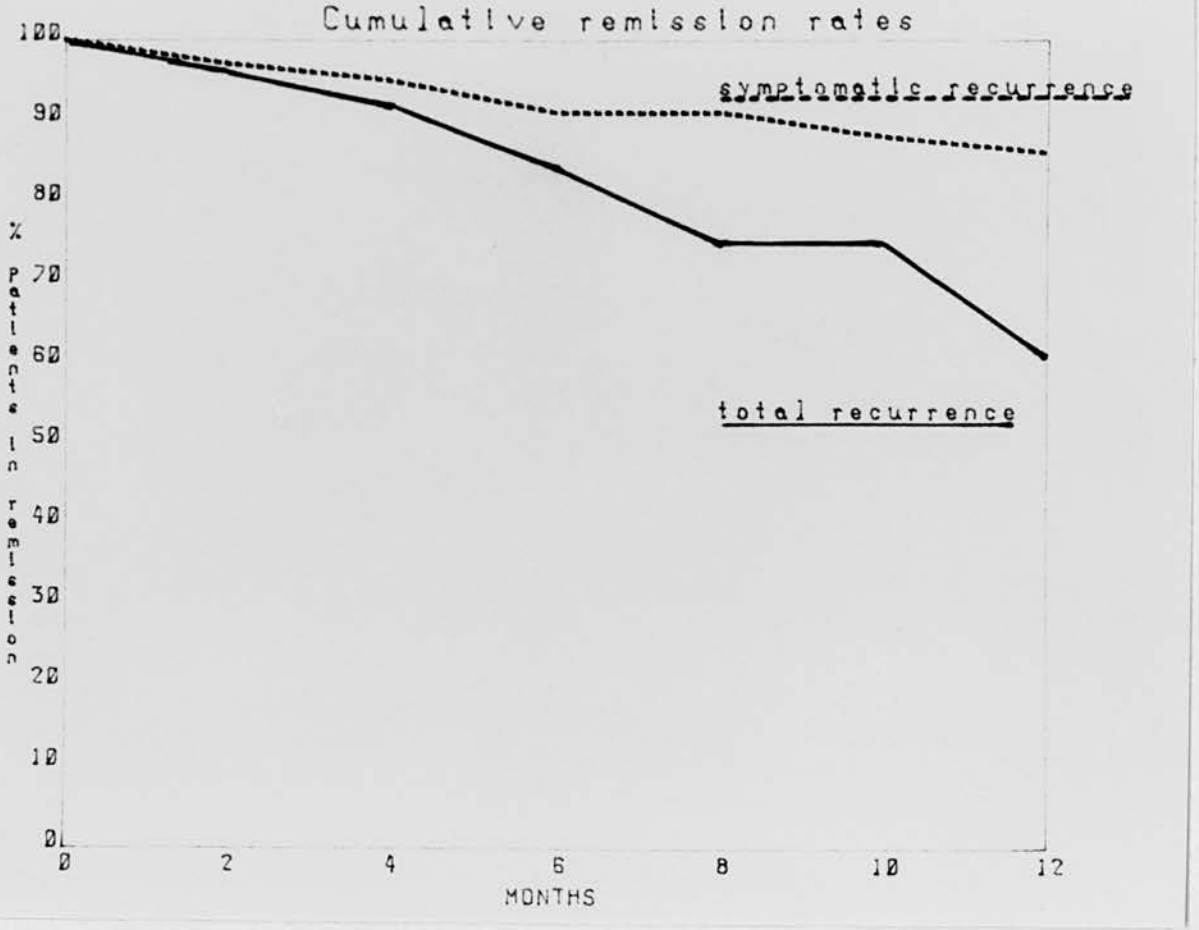
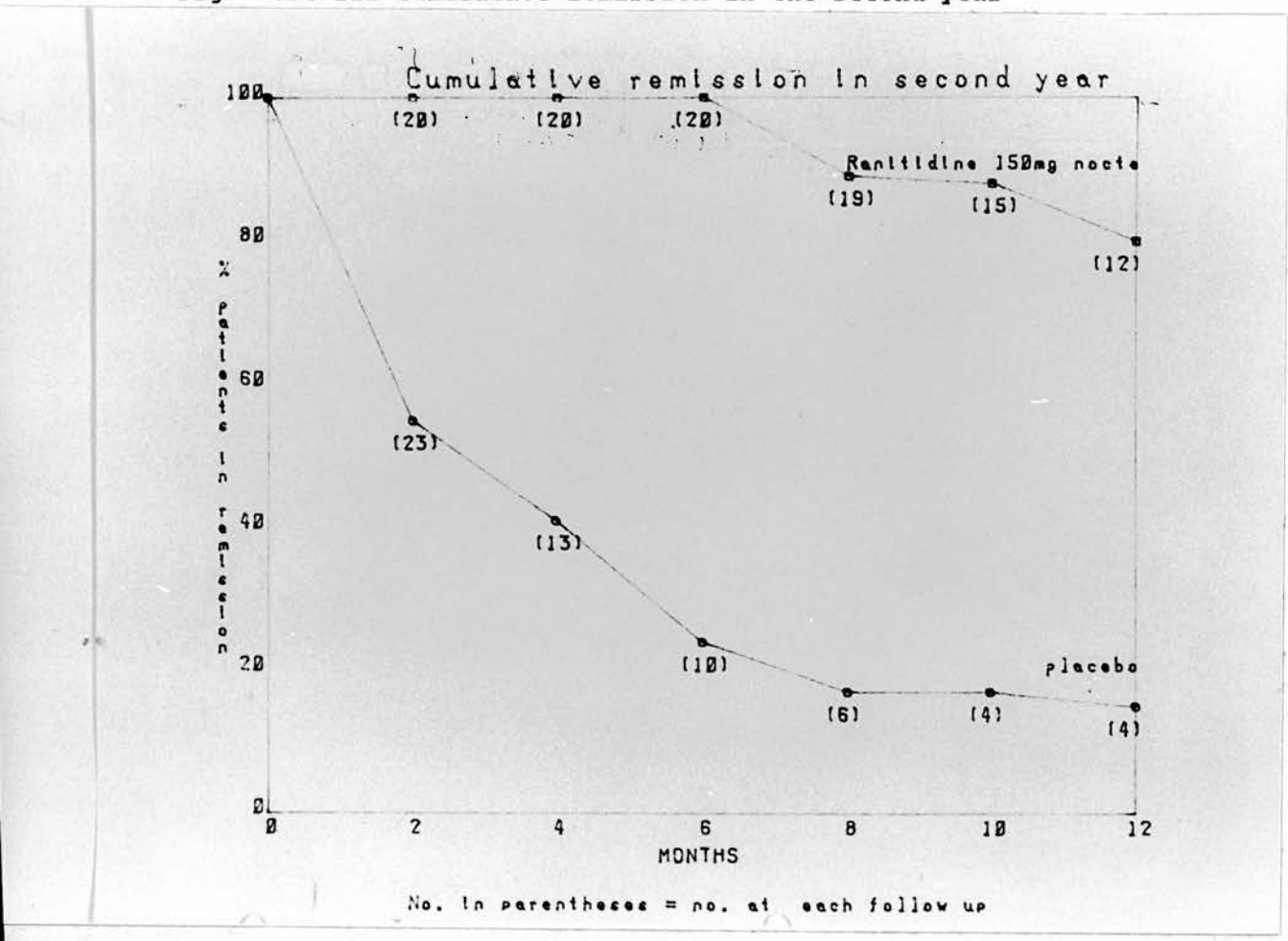


Fig 6.4 III Cumulative remission in the second year



6.5 Discussion

6.5.1 Histamine and Gastric Secretion

The pivotal position of histamine in the control of gastric secretion has been underpinned by the ability of antagonists to the histamine H2 receptor to block secretion stimulated by a number of different pathways.

Unlike a number of other studies (249,293,98,381), a significant difference was not detected in the levels of levels of mucosal histamine between the pre-treatment ulcer groups and the control group. This may, in part, be a reflection of the relatively small numbers recruited to the study. It is not clear whether the change in HMT concentrations in the ranitidine group after four weeks of therapy was due to the ulcer having healed, which it did in all nine patients, or was attributable to a direct effect of the drug. Unpublished studies, carried out in our laboratory, demonstrated that both ranitidine and cimetidine may both stimulate and inhibit the activity of HMT, according to the concentration of the drug.

6.5.2 CM 57755

Despite the apparently sustained action of CM 57755 in some of the early animal studies referred to in Ch 5.2, the results of the secretory study indicate that 600mg of CM 57755 exerts an almost identical gastric inhibitory effect on nocturnal secretion of acid and pepsin, and on daytime acid concentration as the same dose of cimetidine. When assessed by median nocturnal acid output, both drugs inhibited acid secretion by about two thirds, while pepsin secretion was unaffected. In view of the equipotency of the two drugs, it seems likely that CM 57755 will heal ulcers and maintain remission in a manner similar to cimetidine. Since

the gastric inhibitory efficacy implies no therapeutic advantage or disadvantage compared with cimetidine, any role for the new drug will be determined by the presence or absence of unwanted side effects in man, about which no information is yet available.

6.5.3 ICI 162,846

The second secretory study, with ICI 162,846 shows that this is a powerful inhibitor of gastric secretion, capable of abolishing nocturnal secretion of acid and pepsin. It has previously been shown that nocturnal administration of cimetidine (67), ranitidine (186) and famotidine (402) heals 70-80% of duodenal ulcers within four weeks and that nearly all ulcers heal after eight weeks of treatment with H2 receptor antagonists administered before sleep (175). The efficacy of nocturnal treatment is probably because these drug schedules inhibit nocturnal gastric secretion which may, perhaps, be the principal pathophysiologic abnormaltiy in duodenal ulcer disease (164).

The finding that increasing doses of ICI 162,846 produce a modulated range of increases in the range of gastric secretory inhibition is important since there is, as yet, no agreement about the degree of interference with gastric secretion which is therapeutically desirable. On the one hand, 0.5mg of ICI 162,846 produced a degree of inhibition of nocturnal gastric secretion which is analogous to that observed in response to currently available H2 receptor antagonists (399), while a dose of 5mg resulted in inhibition which was as good as, or better than, the inhibition achieved with 80mg of loxtidine (54) or 20-40mg of omeprazole (401,410), the most powerful gastric inhibitors studied to date.

While long-term treatment with cimetidine or ranitidine did not produce neoplastic lesions in rat stomachs, long-term treatment of rats with loxtidine and omeprazole resulted in neoplastic gastric lesions, perhaps because the degree of inhibition produced by these latter drugs was too severe (416,59). The search continues for drugs which can improve ulcer healing and maintenance rates, while not posing a threat to the integrity of the gastric mucosa in the longer term. The graded gastric inhibition achieved with different doses of ICI 162,846 provides a potential choice for the clinician who may require a range of therapeutic efficacy, from partial inhibition for the healing and maintenance of duodenal ulcers (55) to temporary complete abolition of gastric secretion for the prevention of stress ulceration in intensive care units (378) and of Mendelson's syndrome during labour (307).

6.5.4 Ulcer Healing in Service Personnel

In the general population, the healing rate of duodenal ulcer in response to an optimal dose of cimetidine is approximately 80% in four weeks, with a healing rate on placebo of about 35% (41,277). In patients attending two British military hospitals, however, the six week heal-rate in response to cimetidine has been reported as 21% and 27% (154,326) and peptic ulcer remains the single most common cause of invaliding from the British Army (365). The clinical trial of a new H2 receptor antagonist in this population therefore imposes a severe test of the capacity of the drug to heal ulcers.

The finding of a placebo healing rate of 7.7%, only a quarter of that found in most published series, is evidence of the relative intractability of the ulcer diathesis in this population. Viewed in this light the healing rates achieved are, in fact, quite impressive.

The data which might contribute to persistence of ulceration were examined. A previous study (158) suggested an association between ulceration, age of onset, smoking and alcohol consumption. Although this study recruited a young population (average age 30 years), no evidence was detected within the group of an association between age and responsiveness to therapy. More surprisingly, no evidence was found to support an association between smoking and resistance to treatment. It may be that the high percentage of smokers in the study (71%) produced a "blanket" effect, obscuring differences between the sub-groups.

Compliance has always been difficult to assess accurately in this type of trial. Within the limits of a simple tablet count, a compliance rate of around 90% was good compared to established standards (303), yet no association was found. No attempt was made in this study to differentiate the non-responders into those with and those without symptoms when studying the effect of compliance on healing.

6.5.5 Ulcer Maintenance

Previous controlled studies have shown that maintenance treatment with nocturnal ranitdine 150mg is as effective as cimetidine 400mg at night (52,142) and significantly better than placebo (52,180) in preventing duodenal ulcer recurrence during year of treatment. The cumulative recurrence rate of 38% which is observed in this study in the first year of open maintenance treatment is similar to reported values, summarised in a review of studies from many centres throughout the world, in which the average 12-month recurrence rate for all centres was 32%, with a range of 16-52% (52). Since the recurrence rate during the second year of maintenance treatment was less than half that observed

during the first year of maintenance, it seems that ulcers that remain healed during the first twelve months of maintenance treatment tend to remain healed if treatment is continued.

The most significant conclusion to be derived from this study has important implications for the management of ulcer disease. The pattern of ulcer recurrence in patients receiving placebo is different from that observed in patients whose ulcers recur while they are receiving ranitidine. During active maintenance treatment ulcers which recurred were clinically mild and often asymptomatic whereas recurrences in patients receiving placebo were usually symptomatic and associated with a significantly higher incidence of bleeding.

Although it might be argued that these findings could be explained by assuming that one year of maintenance therapy with ranitidine had worsened the natural history of duodenal ulcer disease, so that when treatment was stopped the recurrences were more aggressive than if the patient had received no therapy other than a short healing course of treatment. This explanation is unlikely however, since the percentage of ulcers which recurred during the second year of follow-up, after randomisation to placebo, was of the same order as published values (42, 32,168,17,263,157,99,68) for ulcer recurrence in the placebo limb, after a short course of healing therapy only.

Table 6.5 I summarises the results of seven of these studies (42, 32,168,17,263,157,99), with details of recurrences on placebo and on cimetidine, from which it may be seen that the pattern of ulcer recurrence during the first year after ulcer healing in patients who received placebo or cimetidine was very similar to that found in this study. It appears, therefore, that one year of maintenance treatment with ranitidine has not altered the natural history of duodenal ulcer

disease. If one compares the proportion of symptomatic recurrences in the placebo and active groups in Table 6.5 I, it is apparent that asymptomatic recurrence is more common in the active treatment group. Indeed, when the results of maintenance therapy with placebo is compared with cimetidine 400mg or 400mg twice daily (63) the ratio of asymptomatic to symptomatic is higher with the higher dose of cimetidine (Table 6.5 II). The conclusion drawn, therefore, is that the high proportion of asymptomatic ulcer recurrences in clinical trials is predominantly a phenomenon of active therapy with H2 receptor antagonists, although the reason(s) why these patients remain pain- or complication-free has not yet been defined.

In addition to being symptomatic, recurrences on placebo are significantly more likely to haemorrhage than are recurrences in patients receiving active therapy. Since haemorrhage is an important cause of ulcer-related mortality and morbidity (46), it is apparent that maintenance treatment with ranitidine is safer than no therapy. The policy of treating each ulcer relapse on an interim basis (18) does not seem justifiable since patients are thus exposed to higher risks of potentially fatal complications.

Table 6.5 I **Recurrence rates in double-blind maintenance studies of cimetidine and placebo in patients with duodenal ulcer**

	Cimetidine		Placebo		Haemorrhage	
Reference	Symp	Asymp	Symp	Asymp	Cimetidine	Placebo
42	4	2	23	7	0	4
32	2	0	16	2	0	0
168	3	3	17	8	0	0
17	4	3	18	4	0	0
263	1	5	14	0	0	1
157	1	0	16	2	0	0
99	4	1	13	1	0	0
Total	19	14	117	24	0	5

Table 6.5 II **Symptomatic and asymptomatic recurrrences in patients receiving cimetidine (400mg twice daily or 400mg at night) vs placebo in the maintenance treatment of duodenal ulcer**

Treatment	Symptomatic	Asymptomatic	Ratio symp/asymp
Cimetidine 400mg x2/day n=184	28	25	1.1/1
Cimetidine 400mg at night n=179	31	14	2.2/1
Placebo n=333	178	41	4.3/1

7 OMEPRAZOLE

7.1 Introduction and Pharmacology

Omeprazole is a substituted benzimidazole of molecular weight 345.42 and a solubility in water of 0.1mg/ml. The molecular structure is shown in Fig 7.1 I. Omeprazole is acid labile, subject to breakdown by gastric acid and the compound has therefore been formulated as enteric coated granules in a gelatin-coated capsule, although this type of preparation delays absorption (184). Metabolism is both by reduction, forming a hydroxy compound and oxidation, which forms a sulphide and a sulphone. Only trace amounts of the original compound are detectable in urine and faeces.

Once absorbed, omeprazole is approximately 90% bound to plasma proteins, with a very variable time period from administration to peak plasma concentration (Tmax) depending mainly on the formulation in which the drug is administered - see Table 7.2 I

An H+/K+ dependent ATPase has been shown to be localised to the microvilli of the secretory canaliculi of the gastric parietal cell (332) and is proposed as the likely candidate for the role of the "proton pump". Unlike cholinergic and H2 receptor antagonists, which modulate the behaviour of the pump indirectly, omeprazole acts upon this enzyme system by direct inhibition (117). In isolated gland preparations, omeprazole not only inhibits acid formation (105,118) but also results in a reduction in the level of a phosphoenzyme intermediate (28), indicating a direct action of omeprazole on H+/K+ ATPase.

In animal models, cimetidine inhibits histamine-stimulated acid secretion competitively, but omeprazole inhibits acid stimulated by histamine, pentagastrin and carbachol in a non-competitive fashion (396). In view of these findings and the efficacy of this drug in a

number of animal models (232), studies were undertaken with this drug in healthy volunteers and patients with peptic ulcer. At the time that these studies were carried out the optimal therapeutic dose in duodenal ulcer had not been established. As part of the secretory studies in healthy volunteers the opportunity was also taken to examine the pharmacokinetics, as this had not been undertaken with this formulation at the dosage of 40mg or by the intraduodenal administrative route.

7.2 Pharmacokinetics

7.2.1 Introduction

One part of this study examines the effect of repeated oral dosing on drug absorption and kinetics. The other part of the pharmacokinetic data was obtained during pentagastrin stimulation, when a suspension of the drug was introduced directly into the duodenum through a naso-duodenal tube.

7.2.2 Subjects and Modifications to Methods

Table 7.2 II **Demographic data**

Volunteers	Median	Range	Study (n)
	22	21 - 22 yrs	Overnight 40mg
	76.1	55.0 - 87.3 kg	(6)
	21	20-24 yrs	Pentagastrin 40/80mg
	79.0	55-87 kg	(6)

In the first study 6 male subjects underwent sequential venesection on the first and seventh day after dosing with omeprazole 40mg orally once daily before breakfast. Five mls of venous blood were withdrawn at 1.0,1.5,2.0,2.5,3.0,3.5,4.0,5.0,6.0,7.0,8.0,9.0,10.0,11.0 and 12.0 hours after dosing. In the second study, venous blood was withdrawn from 6

healthy male subjects during the pentagastrin-stimulated secretory studies at 0,10,20,30,45,60,90,120 and 180 mins. following intraduodenal administration of omeprazole 40mg/80mg or placebo on three separate occasions. The blood was placed in heparinised tubes, centrifuged and the supernatant placed in two containers with 20 microlitres of sodium carbonate. These containers were coded numerically in random fashion and stored at -20 degrees C.

The frozen, coded samples were transferred to the Department of Analytical Chemistry at Astra Pharmaceuticals in Sweden, where analysis was undertaken by liquid chromatography and ultraviolet spectrometry (222). Results were then forwarded to Dundee, where the code was broken and mean values between paired samples obtained.

Plasma values thus obtained (micromol/l) were plotted on the y-axis for each individual, against time on the x-axis. The area under the curve (AUC), calculated using the trapezoidal rule, was then obtained at 3 (intraduodenal) and 12 (oral) hours post dose. AUC was expressed as mean $\pm$ SEM and correlated with the degree of inhibition of gastric secretion (acid, pepsin and volume). Tmax was calculated in minutes for each individual and a median value obtained for the group.

7.2.3 Results

Intraduodenal study - at 180 mins. after administration of 40mg the AUC was 2.21 $\pm$ 0.29 micromol/hr/l and 5.25 $\pm$ 1.47 micromol/hr/l with 80mg (Fig 7.2 I).

Oral study - mean values for AUC with 40mg at day 1 and day 7 were 3.40 $\pm$ 2.06 and 4.72 $\pm$ 1.77 micromol/hr/l respectively.

No relationship could be demonstrated between output or percentage inhibition of acid, pepsin or volume and either AUC or log10 AUC in the

intraduodenal study. The correlation coefficient (r) for %inhibition and AUC was -0.34 (acid), 0.02 (pepsin) and -0.26 (volume) with 40mg Day 1 and -0.39 (acid), 0.03 (pepsin) and 0.35 (volume) with 40mg Day 7.

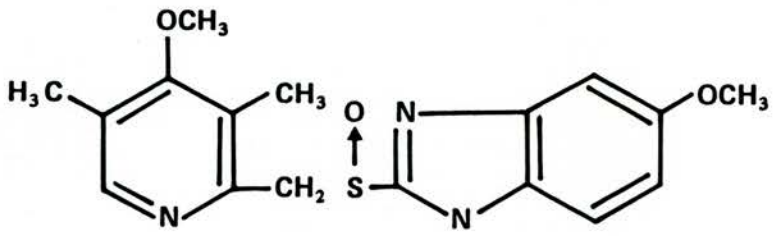
In the 40mg oral dosing study, again no strong correlation was observed between AUC and acid (r=0.72) although this value was a little higher (0.82) with pepsin and just achieved significance at the 5% level.

Table 7.2 I **Formulation and Pharmacokinetics of Omeprazole**

Study	Formulation	Tmax (median mins.)	AUC (mean ± SEM micromol/l/hr)
Inv. Manual (184)	60mg buffered susp. fasting	20	4.83 ± 1.48
	60mg buffered granules no gelatin capsule	20	4.34 ± 0.58
	60mg buffered granules with gelatin capsule	38	4.30 ± 1.25
	60mg e.c.granules fasting	165	4.30 ± 1.51
	60mg e.c.granules with food	300	2.89 ± 1.13
Howden (171)	30mg e.c.granules Day 1 with gelatin capsule	75	3.23 ± 0.83
	30mg e.c.granules Day7 with gelatin capsule	165	5.84 ± 1.28
	60mg e.c.granules Day 1 with gelatin capsule	105	8.82 ± 1.68
	60mg e.c.granules Day 7	135	17.31 ± 1.91
Prichard (310)	40mg e.c.granules Day 1 gelatin capsule a.m. dose	180	1.20 ± 0.70
	40mg e.c.granules Day 5 gelatin capsule a.m. dose	174	2.26 ± 1.24
	40mg e.c.granules Day 1 gelatin capsule p.m. dose	288	0.87 ± 0.58
	40mg e.c.granules Day 5 gelatin capsule p.m. dose	198	2.35 ± 1.65
Wilson (409)	40mg suspension intraduodenal	7.25	2.21 ± 0.29
	80mg suspension intraduodenal	15	5.25 ± 1.47
	40mg e.c.granules Day 1 gelatin capsule		3.40 ± 2.06
	40mg e.c.granules Day 7 gelatin capsule		4.72 ± 1.77

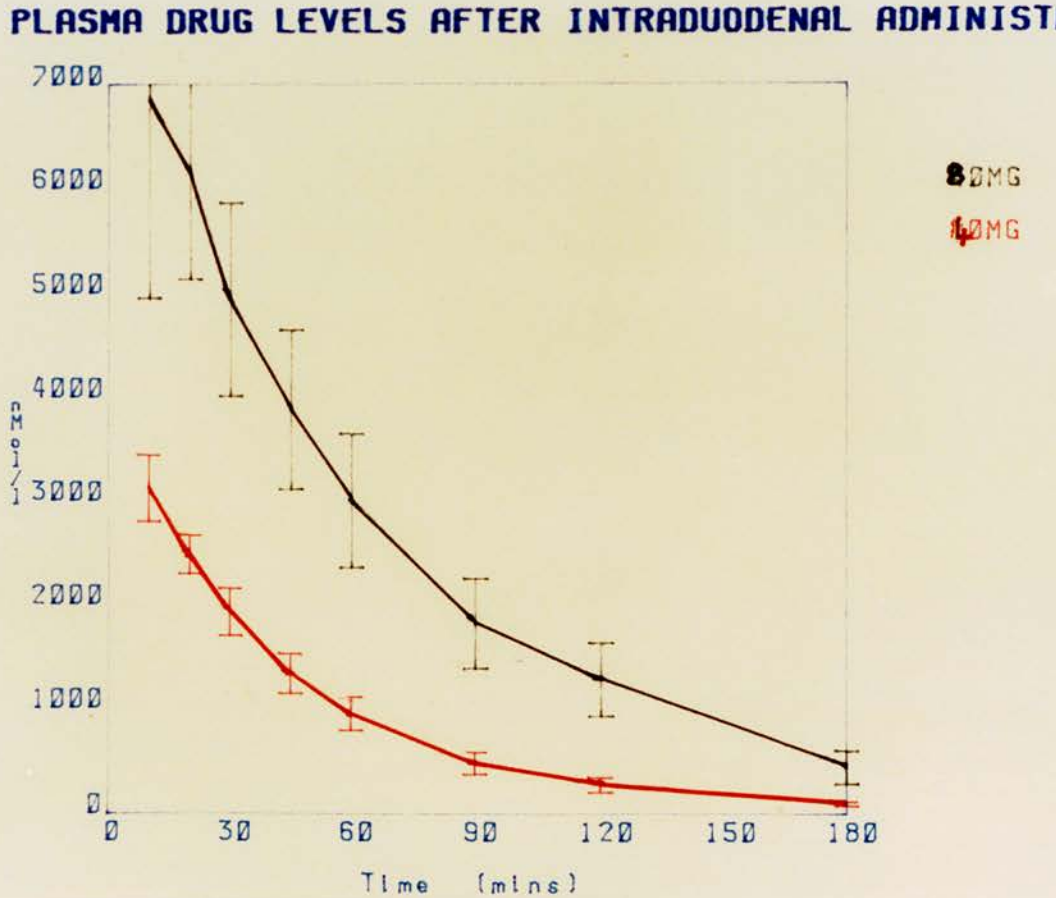
Fig 7.2 I Molecular structure of omeprazole

STRUCTURAL FORMULA



Omeprazole

Fig 7.2 II Plasma drug levels after intraduodenal Study



7.3 Gastric Secretory Studies

7.3.1 Introduction

The effect of omeprazole on gastric secretion was studied in healthy volunteers, during the pharmacokinetic studies, and in duodenal ulcer patients receiving therapy. In volunteers nocturnal secretion was studied following 30, 40 and 60mg orally and pentagastrin-stimulated secretion was studied after 40 and 80 mg intraduodenally. The effect of 30 and 60 mg of omeprazole on overnight and pentagastrin-stimulated gastric secretion was examined in patients with duodenal ulcer.

Table 7.3 I **Demographic data**

	Median	Range	Study (n)
Volunteers	21	21 - 22 yrs	Overnight 30/60mg
	78	70 - 85 kg	(6)
	21	20 - 24 yrs	Overnight 40mg
	76.1	55 - 87 kg	(6)
	22	20-24 yrs	Pentagastrin 40/80mg
	74.6	65-83 kg	(6)
Patients			
	39	19-66 yrs	Overnight 30/60mg
	72.2	51-88 kg	(11)
	39	25-57 yrs	Pentagastrin 30/60mg
	78.2	65-101 kg	(10)

Inclusion criteria:

Subjects
- aged 18 to 40 years
- normal physical examination and laboratory values
- no significant illness in the preceding two weeks
- no concomitant medication and no investigational drug in the preceding four weeks
- no cardiac, renal , hepatic or gastrointestinal disease (including a histroy of dyspepsia)
- no history of drug addiction or alcohol abuse

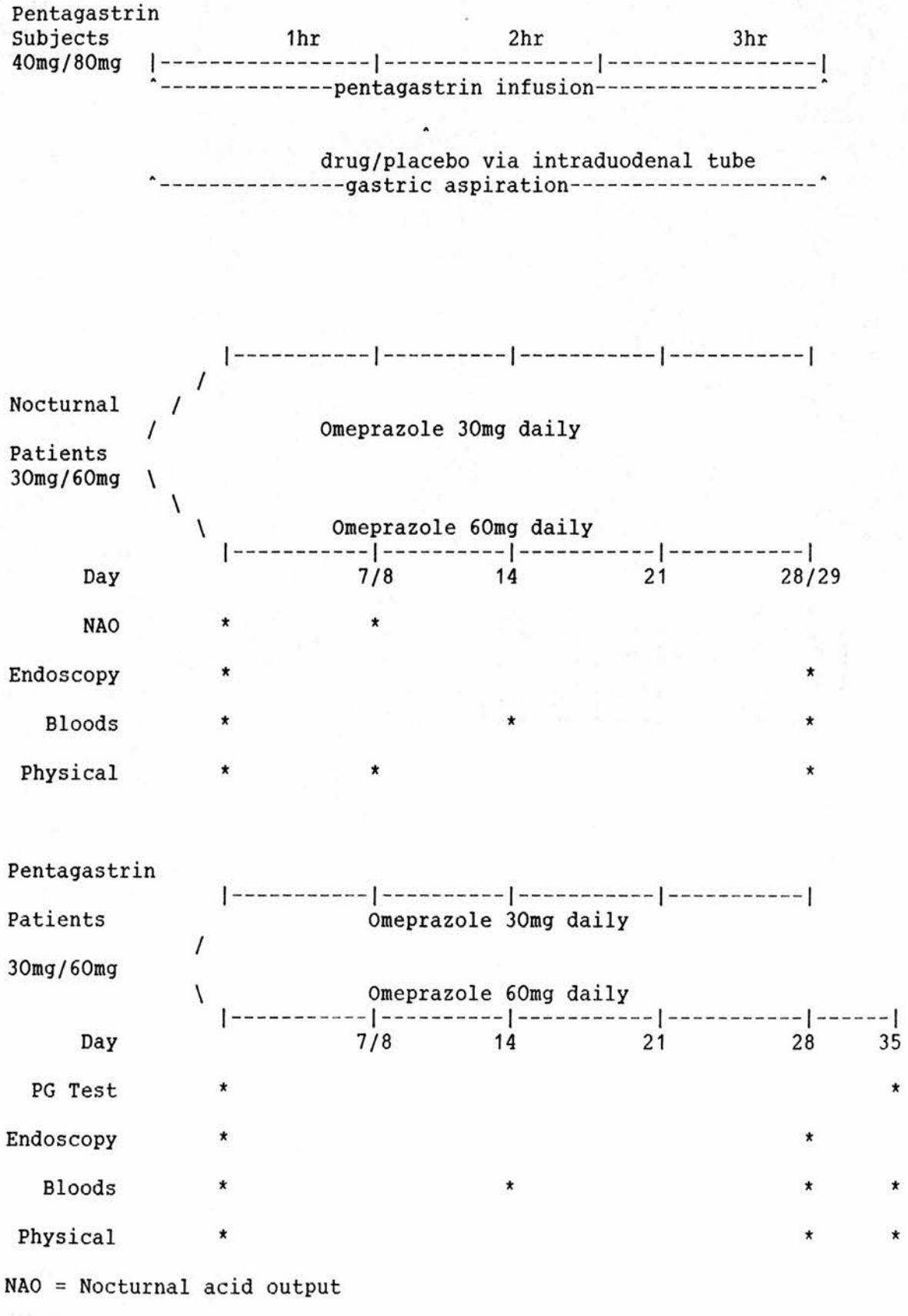
Patients
- aged 18 to 70 years
- male
- active duodenal ulcer, verified by endoscopy not more than 5 days previously
- no gastric or prepyloric ulcers and no pyloric stenosis
- no previous gastric surgery
- no concurrent disease which would potentially complicate the evaluation of the drug
- no significant abnormality in laboratory values
- treatment with H2 receptor antagonists, anticholinergics or other antisecretory drugs in the previous two weeks
- those whose ulcers had not healed during 8 weeks full therapy with H2 receptor blocking drugs
- those unlikely to co-operate in the trial

Study Design:
Nocturnal
Subjects 30mg/60mg

	omeprazole			omeprazole	
Day		7/8	14	21	28/29
NAO	*	*			*
Physical	*	*			*
Bloods	*	*			*

Nocturnal Subjects 40mg

Day		1	2	3	4	5	6	7
NAO	*	*						*
Bloods	*	*						*
Physical	*	*						*



NAO = Nocturnal acid output

PG = Pentagastrin

In summary, therefore, six healthy volunteers received received omeprazole 30mg and 60mg daily for two treatment periods of 7 days, in random order, separated by 15 days. Nocturnal gastric secretion was then measured before and at the end of each treatment period. Six healthy volunteers received omeprazole 40mg daily for one week, with nocturnal gastric secretory studies before treatment, on day 1/2 and on day 7/8. A third group of volunteers received placebo, 40mg or 80mg in random order via an intraduodenal tube, after the first hour of a three hour secretory study with intravenous pentagstrin stimulation. Twenty one patients with active duodenal ulceration were commenced on therapy with omeprazole 30mg or 60mg daily. Nocturnal secretory studies were performed before, and seven days into, treatment in eleven and pentagstrin tests were performed before and one week after (day 35) four weeks of therapy in ten patients.

7.3.3 Results

Table 7.3.II **Subjects Nocturnal Output** (see also Fig 7.3 I)

		30mg	40mg	60mg
Acid mEq/hr	Pre	3.3 ± 2.9	4.3 ± 1.9	3.3 ± 2.9
	Day 1/2		0.8 ± 1.0 *(81%)	
	Day 7/8	1.7 ± 1.1 *(48%)	0.9 ± 0.4 *(79%)	0.9 ± 0.5 *(73%)
Pepsin mg/hr	Pre	50 ± 16	39 ± 27	50 ± 16
	Day 1/2		17 ± 26 (56%)	
	Day 7/8	47 ± 12 (6%)	34 ± 29 (13%)	39 ± 23 (22%)
Volume ml/hr	Pre	65 ± 19	69 ± 10	65 ± 19
	Day 1/2		34 ± 6 (50%)	
	Day 7/8	55 ± 12 (15%)	41 ± 4 (40%)	47 ± 23 (28%)

Table 7.3.III **Subjects Pentagastrin Output** (see also Fig 7.3 II)

Acid		1hr	2hr	3hr
	Placebo	23.1 ± 9.4	30.5 ± 11.7	25.5 ± 7.0
	40mg	21.9 ± 6.9	9.7 ± 3.3 *(68%)	0.5 ± 0.2 **(98%)
	80mg	23.9 ± 8.2	6.6 ± 0.9 *(78%)	0 **(100%)
Pepsin	Placebo	106 ± 31	134 ± 80	126 ± 32
	40mg	138 ± 60	53 ± 28 (60%)	12 ± 11 **(90%)
	80mg	124 ± 53	29 ± 15 *(78%)	0 **(100%)
Volume	Placebo	246 ± 108		265 ± 117
	40mg	248 ± 60		47 ± 41 (85%)
	80mg	277 ± 106		59 ± 44 (78%)

Table 7.3.IV **Patients Nocturnal Output** (see also Fig 7.3 III)

Acid		30mg	60mg
	Pre	7.3 ± 5.4	6.2 ± 2.1
	Day 7/8	0.4 ± 0.7 *(94%)	1.1 ± 0.7 *(82%)
Pepsin	Pre	51 ±15	46 ±12
	Day 7/8	8 ±14 *(84%)	21 ±9 *(54%)
Volume	Pre	101 ± 39	77 ± 24
	Day 7/8	47 ± 22 (53%)	46 ± 13 (40%)

Table 7.3.V **Patient Pentagastrin Output**

Acid		30mg	60mg
	Pre	45.5 ± 4.9	37.6 ± 3.5
	Day 35	32.9 ± 6.6	34.8 ± 5.0

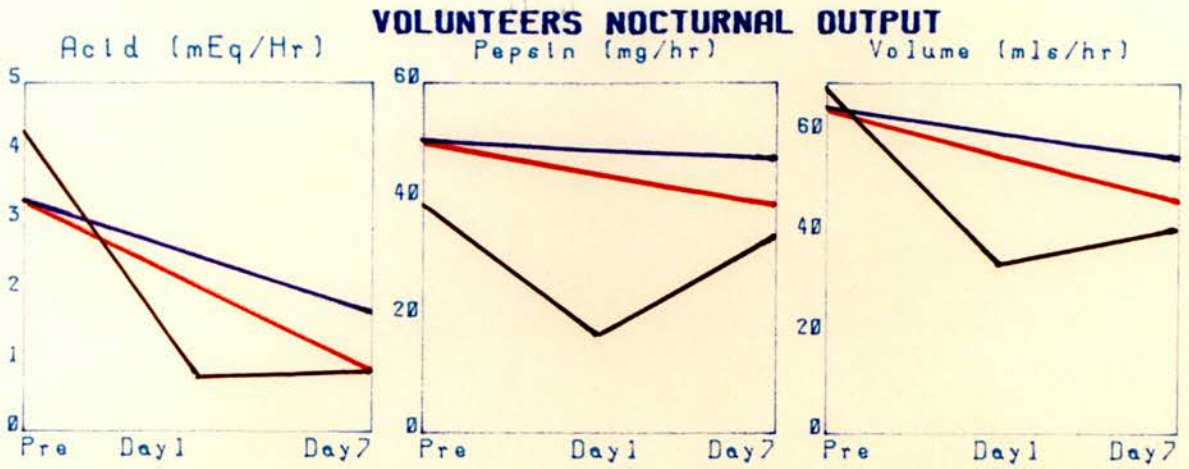
* = $p<0.05$, ** = $p<0.01$, compared to treatment value

In the volunteers, nocturnal acid output fell by (30mg) 46%, (40mg) 79% and (60mg) 70% after seven days and pentagastrin-stimulated acid output by (40mg) 98% and (80mg) 100%. No clear effect was seen on nocturnal pepsin output in volunteers but in patients values were decreased by (30mg) 84% and (60mg) 53%. During pentagastrin stimulation pepsin output fell by the second hour after drug administration to (40mg) 98% and (80mg) 100% of control values.

Acid output in duodenal ulcer patients fell by (30mg) 96% and (60mg) 81%. A further group of ten patients underwent pentagastrin tests before and 7 days after a 28 day course of omeprazole 30mg or 60mg - no significant difference was demonstrated following therapy.

Omeprazole was well tolerated, producing no serious adverse experiences, changes in physical examination or laboratory values.

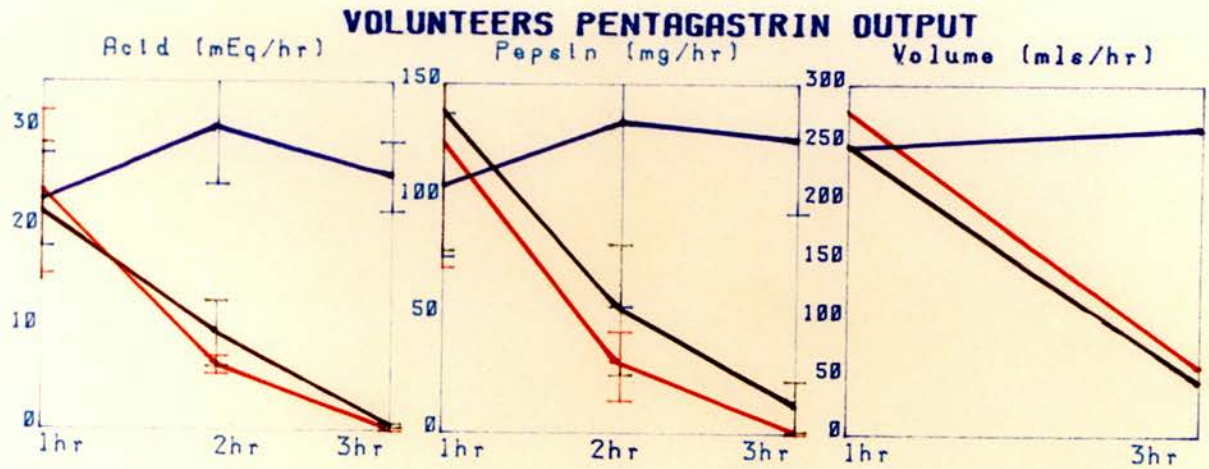
Fig 7.3 I Volunteers Nocturnal Output



3.3		1.7	50		47	65		55
4.3	0.8	0.9	39	17	34	69	34	41
3.3		0.9	50		39	65		47

30mg
40mg
60mg

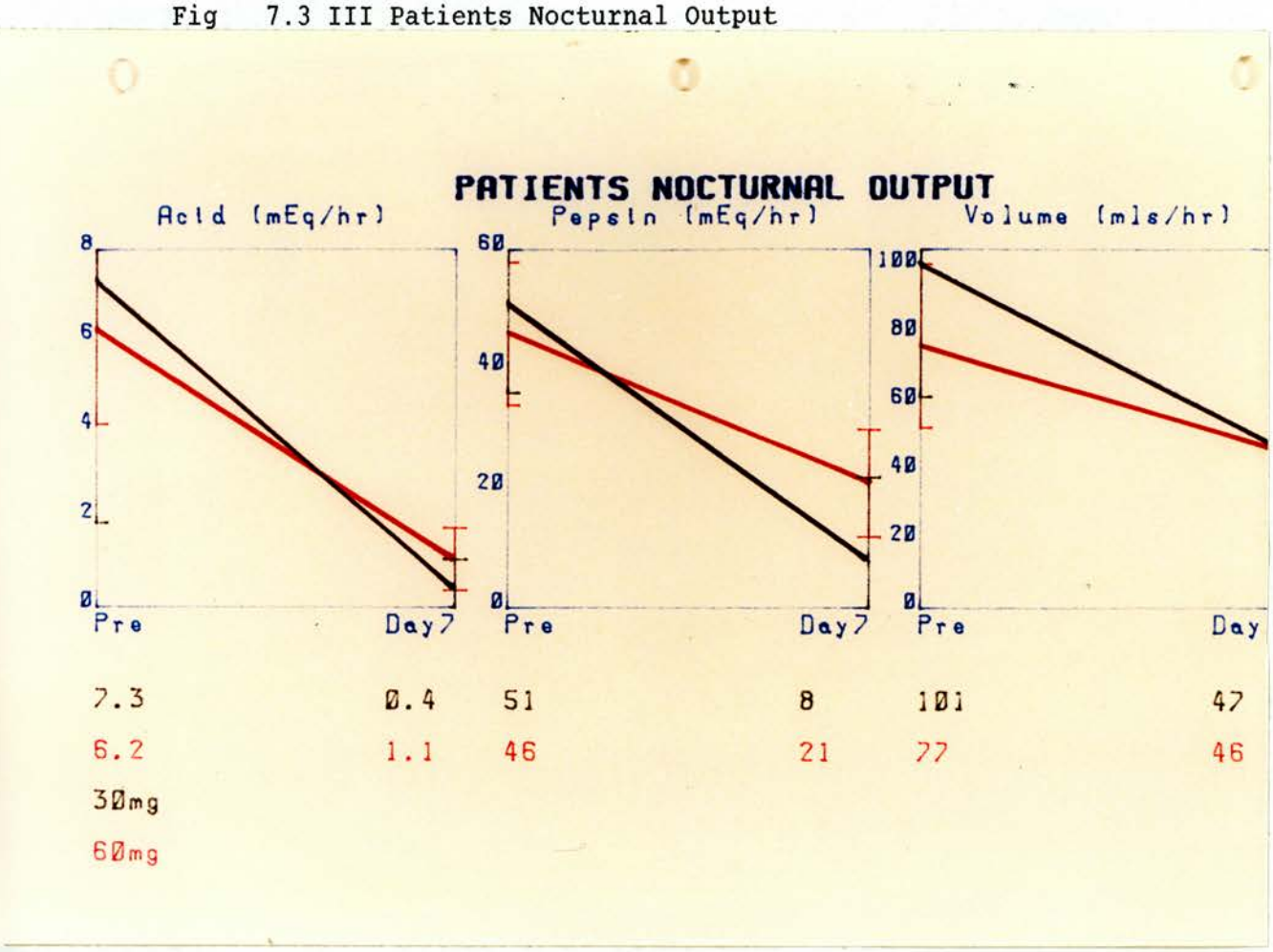
Fig 7.3 II Volunteers Pentagastrin Output



23.1	30.5	25.5	106	134	126	246	265
21.9	9.7	0.5	138	53	12	248	47
23.9	6.6	0	124	29	0	277	59

placebo
40mg
80mg

Fig 7.3 III Patients Nocturnal Output



7.4 Ulcer Healing

7.4.1 Introduction

The foregoing, and other, studies in patients and healthy volunteers have shown that omeprazole produces a dose-dependent inhibition of basal and pentagastrin-stimulated gastric acid secretion which is maximal after five to seven days of treatment (238,72,409). Rapid healing of duodenal ulcers - 93% at two weeks - has been reported with 40mg omeprazole daily (394). Eleven of the patients in the first section of this study formed part of a larger multicentre, dose ranging study of duodenal ulcer healing (72). The main objective was to study the tolerance to and the efficacy of four doses of omeprazole (20,30,40 and 60mg) given once daily over four weeks to heal duodenal ulcers and relieve symptoms. Patients in the second section, with peptic ulcers resistant to healing with H2 recpetor antagonists, also formed part of a larger study of seventeen patients from three different centres (384). Really "resistant" peptic ulcers are not common but, by combining patients from several centres, it was possible to examine whether omeprazole offered any advantage for this therapeutic problem.

7.4.2 Acute Duodenal Ulcer Healing

7.4.2.1 Patients and Modifications to Methods

Twenty one patients with one or more duodenal ulcers, verified by endoscopy in no more than five days before entering the study, were randomised to therapy with omeprazole 30mg or 60mg taken once daily before breakfast at 0800hrs. Demographic data and inclusion criteria have been enumerated in Ch 7.2. and 7.3. Two patients had received a course of cimetidine which had finished four and six weeks before their initial endoscopy. Nineteen of the twenty one had taken some form of

antacid in the previous thirty days. Two patients were receiving a beta-blocking drug for hypertension, two intermittently used a salbutamol inhaler for asthma and one patient was an insulin-dependent diabetic. Fourteen of the twenty one were regular smokers (mean ± SEM 17 ± 2/day).

Symptoms were assessed on days 0,8,15 and 29 and any adverse events recorded. Omeprazole was administered in hard gelatin capsules containing 30mg of omeprazole as enteric coated granules. Drug supplies were renewed and unused capsules returned on days 8 and 15. Eleven patients were randomised to receive 30mg daily and ten patients to 60mg daily. Endoscopic examination of the oesophagus, stomach, first and second parts of duodenum was carried out on days -5 to 0 and 29. Venous blood was withdrawn and endoscopic biopsies of fundus, antrum and duodenum were taken on both occasions. Ulcer healing was taken as complete healing of the ulcer site.

For both the acute and the resistant ulcer healing sections the combined results from the multicentre trial will be given in parentheses, and the discussion sections will refer to the combined results.

7.4.2.2 Results

All eleven (17) patients who received 30mg daily and nine (14) of the ten (15) who received 60mg daily had healed endoscopically in four weeks. The remaining patient, who had three ulcers at the start of the trial, still had symptoms and persistent ulceration at four weeks. All other patients were asymptomatic after eight days of therapy.

When the patients who received 20mg and 40mg were included (12 of 14 healed), this amounted to a total of 43 who completed the four week course of treatment. 41 had healed although, during a subsequent six

months of follow up, 11 of 36 patients had a symptomatic endoscopically proven relapse. The ulcers healed equally well on all four regimens and there was no difference in the relapse rate.

Omeprazole was well tolerated, with no proven drug-related side effects.

7.4.3 Refractory Ulcer Healing

7.4.3.1 Introduction

Rarely, patients with peptic ulceration are resistant to conventional therapy with modern anti-ulcer drugs (417). In view of the reports that omeprazole rapidly heals duodenal ulcers (72,149) and even the more resistant ulcers associated with gastrinomas (226), this study was designed to assess the therapeutic benefit, if any, that omeprazole might confer in the situation where ulcers have persisted for three months or more despite therapy with H2 receptor antagonists.

7.4.3.2 Patients and Methods

Four (17) patients resistant to conventional ulcer therapy were given 40mg omeprazole orally as a morning dose for two to eight weeks until the ulcer had healed. These patients were considered resistant because prolonged therapy with H2 receptor antagonists for at least three months in conventional doses, singly or in combination with other anti-ulcer drugs, had not led to ulcer healing.

Two (10) patients had a duodenal ulcer, two (4) had a gastric ulcer and (3) patients had a stomal ulcer after a Billroth II gastrectomy. Ulcer size (greatest diameter) ranged from 4 to 30mm, with a median of 6mm. No patient was admitted to the trial who had been taking non-steroidal anti-inflammatories. All previous anti-ulcer medication was

stopped the day before starting omeprazole therapy. Endoscopy was performed at the beginning of the study, after two weeks and, if healing was not complete, after a further two and six weeks of therapy. Thus, the maximum duration of therapy in any individual was eight weeks. Patient compliance was assessed by tablet count. All patients were kept under regular endoscopic review after healing was achieved.

7.4.3.3 Results

All therapy in the three months before the study, ulcer history and complications are summarised in Table 7.4 I . All patients had been treated before entry to the trial for three months, and some for more than one year, without achieving ulcer healing.

The three stomal ulcers and two (9) out of two (10) duodenal ulcers healed after two weeks and the remaining duodenal ulcer healed after four weeks of therapy. Gastric ulcer healing was complete in one patient after two weeks, in (1) patient after four weeks and in one (2) patients after eight weeks of therapy.

Only two of the seventeen patients, both with gastric ulcers, still had pain by day 15. One of these, patient 14, was known to suffer from chronic pancreatitis. The other, patient 12, required four weeks of omeprazole to heal his ulcer and his pain resolved shortly thereafter.

Capsule counts ranged from 80% to 100%. Physical examination and laboratory studies remained normal. There were no confirmed treatment-related side effects. Patient 5 developed epididymitis after 24 days of treatment. Patient 12 complained of headache for two days which resolved during continued treatment with omeprazole. Patient 14 had symptoms of an upper respiratory tract infection associated with perioral herpes simplex.

In eleven patients the ulcer relapsed soon after maintenance therapy was substituted for omeprazole (Table 7.4 II). Patients 1 and 14 were rehealed with omeprazole. On 20mg omeprazole daily patient 1 had a relapse within twelve weeks and the ulcer rehealed on 40mg omeprazole daily in two weeks.

Patients 1 and 14 were free from relapse during continuous treatment with 40mg omeprazole daily for more than four months. Using a combination of ranitidine and sucralfate in patient 6, rehealing was not achieved and a highly selective vagotomy was subsequently been performed. Patient 16, for similar reasons, also underwent a highly selective vagotomy.

Table 7.4. I **Demographic data**

Patient	Site	Sex	Age	Ulcer History (years)	Complications	Therapy last 3 mths (mg)	Cigs/day
1	stomal	F	30	1	-	ran 600 pir 150	10
2	du	M	32	15	perforation	ran 300	5-10
3	du	M	45	4	bleed	ran 300 pir 100	-
4	du	F	59	10	-	ran 300	daily
5	du	M	69	20	bleed	cim 800	daily
6	gu(pp)	F	35	13	-	ran 300	15-20
7	du	F	30	10	-	ran 600	30
8	gu	M	61	1)	bleed	ran 300	20
9	du	M	22	5	-	ran 300	-
10	stomal	M	40	4	perforation	ran 300-600	daily
11	stomal	M	34	18	perforation	ran 600	17
12	gu	M	42	7	-	ran 450-750	8
13	du	M	43	10	vagotomy	cim 800-1600	8-10 cigars
14	gu	F	54	0.5	bleed	ran 450	8-10
15	du	F	59	7	-	cim 1000 pir 150	-
16	du	M	49	10	-	cim 1600	-
17	du	M	41	20	perforation	cim 1600	10-15

Table 7.4 II **Healing and follow-up data**

Patient	Site	2 week	4 week	8 week	Maintenance therapy	Duration (weeks)	Relapse +/-
a		healed	healed	-	ran 600	5	
1b	stomal	none	healed	-	omep 20	12	+
c		healed	-	-	omep 40	>16	-
2	du	healed	healed	-	-	>26	-
3	du	healed	healed	-	ran 300 pir 100	3	+
4	du	healed	-	-	ran 300	>26	? (none)
5	du	healed	healed	-	-	>16	-
6	gu(pp)	present	present	healed	ran 300 suc 4g	8	+
						20	surgery
7	du	healed	healed	-	ran 300	48	+
8	gu	healed	healed	-	ran 300	52	-
9	du	healed	healed	-	ran 300	52	+
10	stomal	healed	-	-	ran 300	16	+
11	stomal	healed	-	-	ran 300	38	+
12	gu	present	healed	-	died from myocardial infarct		
13	du	present	healed	healed	cim 1000 suc 4g	27	+
14a	gu	present	present	healed	ran 600	4	+
b	gu	present	present	healed	omep 40	>26	-
15	du	healed	healed	-	ran 300 pir 100	20	-
16	du	healed	-	-	cim 800	6	+ surgery
17	du	healed	-	-	cim 800	12	+

ran = ranitidine omep = omeprazole pir = pirenzepine suc = sucralfate

cim = cimetidine

7.5 Safety Studies

7.5.1 Introduction

At the 1st International Symposium on omeprazole in 1984 the preclinical section referred to 145 published preclinical studies. Only 4 of these addressed some aspect of the safety of the drug although reference was made during several of the presentations to studies which had been carried out assessing the long-term toxicology of high dose omeprazole in rats. A dose-dependent effect was seen at the two year stage with hyperplasia of the enterochromaffin-like (ECL) cells resulting in histological appearances similar to carcinoid. Table 7.5 I is taken from data presented at the International Symposium by Dr R Hakansson. The studies desribed below were initiated before the effect on ECL cells in the rat studies had been noted.

There is no other benzimidazole currently in use in humans as an anti-secretory agent but, in view of the effects previously reported with cimetidine (292,294), it was thought valuable to screen omeprazole for any similar side effects.

7.5.2 Patients and Methods

All 21 patients were male, mean age 40 years (21-66), and 14 were smokers. These patients were diagnosed endoscopically as having an active duodenal ulcer, and entered into a trial of treatment with omeprazole 30mg/60mg daily for four weeks. Two biopsies were taken from three sites - fundus, antrum and duodenum - at the time of the initial and follow up endoscopies. One biopsy from each of the three sites was placed in formalin and sections stained both with standard haematoxylin and eosin, and also subsequently by Grimelsius staining to examine for ECL cells. An assessment of the degree of inflammation was made from the H and E sections by one single pathologist using the following scoring

system : 0=absent, 1=mild, 2=moderate, 3=marked and 4=severe. The second of the paired biopsies was placed in gluteraldehyde and electron microscopy carried out by the same pathologist.

Venous blood for haematology (FBC, diff and platelets) and biochemistry (urea,electrolytes, creatinine, glucose, liver and thyroid function, calcium, phosphate, albumin, protein and urate) was withdrawn on days 0,14,28 and 35. In addition, blood withdrawn at that time was analysed for serum gastrin, sex hormones (FSH, LH, testosterone and prolactin) and lymphocyte responsiveness to PHA and Con-A. All these analyses were undertaken in Ninewells laboratories except the gastrins, which were measured in the Biochemical Dept. of Glasgow Royal Infirmary.

Values obtained are expressed as mean $\pm$ SD, and differences between before, during and after therapy examined by students paired 't' test.

7.5.3 Results

The mean inflammatory score for 21 patients fell from 1.7 $\pm$ 1.2 to 0.9 $\pm$ 0.9 in the duodenum ($p<0.02$) and from 2.0 $\pm$ 0.8 to 1.1 $\pm$ 0.8 in gastric antrum ($p<0.01$). The corresponding score for gastric fundus remained with no significant change from 0.4 $\pm$ 0.6 to 0.9 $\pm$ 1.1.

Electron microscopy revealed no evidence of cellular damage, a slight increase in inclusion bodies and a definite increase in tubular vesicle formation. Grimelsius staining revealed no alteration in the density of ECL cells.

In one patient, haemoglobin was initially depressed at 9.4g/dl but reverted to within the normal range during the four weeks of treatment. Tables 7.5 II,III and IV contain the values for serum gastrin, sex hormones and lymphocyte responsiveness. Serum gastrin, although remaining within the normal range, was significantly elevated ($p<0.01$)

during and following treatment with a trend to peaking during treatment and falling after therapy was stopped, although there was no significant difference between days 14, 28 and 35.

Table 7.5 I **No. of carcinoids in rats**

	Male	Female
vehicle	0/120	0/120
40 micro mol/kg	0/60	14/60
125 "	1/60	19/60
400 "	6/60	24/60

Table 7.5. II **Gastrin** (N<45pmol/l)

	Pre	Day 14	Day 28	Day 35
30mg	5.4 ± 2.3	35.1 ± 11.1	26.9 ± 22.1	26.7 ± 21.4
60mg	5.9 ± 3.2	27.2 ± 23.1	35.7 ± 20.6	18.6 ± 11.2

Table 7.5 III **Sex hormones**

Testosterone (10-40 nmol/l)

30mg	33.1 ± 10.5	22.1 ± 7.8	21.2 ± 3.0	31.1 ± 15.1
60mg	24.1 ± 4.6	28.4 ± 8.2	29.3 ± 8.1	28.7 ± 5.9

Prolactin <300 m.i.u./l

30mg	305 ± 301	268 ± 234	398 ± 409	266 ± 243
60mg	140 ± 36	129 ± 44	150 ± 73	183 ± 70

FSH (<40yrs 0.5 - 3.9, >40yrs 0.5 - 7.2 m.i.u./l)

30mg	3.7 ± 3.5	3.3 ± 3.7	2.7 ± 2.6	3.6 ± 3.0
60mg	3.3 ± 2.8	4.0 ± 2.4	2.8 ± 1.4	4.1 ± 3.3

LH (<40yrs 0.5 - 6.8, >40yrs 1.8 - 7.0 m.i.u./l)

30mg	5.9 ± 1.9	5.9 ± 2.4	5.4 ± 1.2	6.3 ± 1.5
60mg	4.4 ± 1.4	5.5 ± 1.6	5.3 ± 1.8	4.9 ± 1.8

Table 7.5 IV **Lymphocytes** (65-95% cells responding)

30mg	84 ± 10	86 ± 4	84 ± 6	85 ± 3
60mg	78 ± 9	76 ± 10	77 ± 8	81 ± 7

7.6 Discussion

7.6.1 Pharmacokinetics

A number of studies have now been published about the pharmacokinetics of omeprazole and these are summarised in Table 7.6 I. It can be seen that several other factors, in addition to dosage level, influence plasma drug levels achieved: formulation, pre/post - cibal, morning or evening administration and single or multiple dosing. It has been suggested both by Howden et al (171) and Prichard et al (310) that omeprazole increases its own bioavailability through effecting an increase in intragastric pH, thus reducing the breakdown of omeprazole within the stomach.

The data from Howden et al are particularly interesting in view of the long term effect of high doses of omeprazole in rats. In this situation, a number of ECL - type tumours have been noted. If the data from Howden's study are plotted with AUC against time (Fig 7.6 I) it can be seen that the slope of the line increases as the dose is increased. Thus higher doses of the drug achieve disproportionately higher plasma levels.

The evidence for a positive correlation of AUC to inhibitory effect is conflicting - the current studies and those of Howden et al do not support this although Lind et al (238) obtained a correlation coefficient of AUC against % inhibition of acid of 0.93. It may be, of course, that since higher doses of omeprazole were used both in this study and in the work by Howden, that all the points plotted were in the upper portion of the curve.

As might be expected, absorption was most rapid when a suspension of the drug was instilled into the duodenum. Although the addition of a gelatin coat to the enteric coated granules slighltly delays absorption,

the ease with which the drug can be administered in this form justifies this formulation for clinical use, particularly as good healing rates are achieved.

7.6.2 Secretory studies

In the secretory studies, the group mean hourly acid outputs show that omeprazole has a marked inhibitory effect on both healthy subjects and patients. When the individual results are examined, the reduction in acid output (with one exception) is dose-related at the 30mg and 60mg doses in volunteers. This is in accord with another study (85) with 30mg and 60mg, which demonstrated a reduction in mean concentration of acid in gastric contents sampled during the night by 51% and 67% respectively. Neither the 40mg group nor the two patient groups can be commented on in this regard as individuals in these groups only received therapy at a single dose level. The patients had a higher mean acid output before therapy, which accounts for the greater percentage inhibition, although there was no statistically significant difference between the pre-treatment levels for the three groups.

The mechanism of reduction in gastric acid output has been investigated by plotting the percentage of reduction in gastric acid concentration against the percentage reduction in secretory volume for subjects and patients (Fig 7.6 II). If the effect of omeprazole was equal on concentration and volume then all the points would lie on the intersecting line. As the majority of the points (17 of 22) are displaced towards the vertical axis, it can be seen that the major effect of omeprazole is on acid concentration with a smaller effect on volume.

The results with pentagastrin stimulation in volunteers confirm the observations in a previous study (238) that omeprazole is a powerful inhibitor of gastric secretion in this setting. There is only a short lag before the drug exerts an inhibitory effect although clearly, since omeprazole was introduced into the duodenum, this effect must be through a systemic action. In patients, the method of examining the effect of omeprazole on pentagastrin stimulated secretion was not comparable but the results clearly demonstrate a return of acid secretion to within control levels, seven days after a twenty eight day course of therapy. Similar studies have been carried out at other centres (72) and have demonstrated that, at day twenty eight, acid output was inhibited with 60mg and 30mg by 94% and 81% respectively.

The effect of omeprazole on pepsin secretion is less clear. It does appear, however, that in the study using 40mg, an early reduction on day 1/2 is not sustained at day 7/8. This is in contrast to the duodenal ulcer patients in whom a substantial reduction of 84% and 54% of pre-treatment pepsin output is seen after seven days of therapy. The fall in pepsin secretion to zero in volunteers during pentagastrin stimulation is much more likely to be secondary to inhibition of volume rather than any direct effect on chief cell function.

7.6.3 Ulcer healing

Since omeprazole is a powerful inhibitor of gastric secretion, the drug has been used to heal ulcers. Omeprazole 20-60mg daily for four weeks achieved healing in 41 of 43 patients (95%). This compares well with other studies which report a four week healing rate of 84% with 40mg (18) and 96% with 20/60mg (149). In early open trials, both with cimetidine and ranitidine, healing rates of 78-94% have been reported

(16,61). It is generally now accepted, however, that the proportion of patients who heal after four weeks of H2 receptor blockers is around 70-80% (112,7).

It is not surprising that 31% of the ulcers followed up in this study relapsed within six months. The actual figure might well have been higher as only symptomatic patients were re-endoscoped. Cumulative incidences of ulcer recurrence after successful healing with H2 antagonists have been reported at between 50% and 60% (19,63,218,185).

7.6.4 Refractory ulcers

The study of patients with refractory ulcer has shown that treatment with omeprazole 40mg daily healed peptic ulcers which had persisted during many months of conventional therapy. These ulcers have been defined as resistant or refractory (306,20). Resistant duodenal and stomal ulcers healed particularly rapidly in this study during treatment with omeprazole. In this respect, our findings compliment the study (226) in which omeprazole has been shown to heal ulcers in patients with the Zollinger-Ellison syndrome in whom treatment with H2 receptor antagonists had become unsatisfactory.

Perhaps predictably, 65% of the group have so far relapsed. Clearly, this value may alter with continued follow-up. The optimal therapeutic management of these patients is not clear.

Recent reviews (417,9) have suggested that, when an ulcer is resistant to one of a group of drugs, it is often necessary to change to a drug of a different type. If medical treatment has failed to heal the ulcer, surgical treatment, such as vagotomy plus antrectomy, is usually required to control the ulcer disease. However, in view of the problems associated with the surgical treatment of resistant ulcers (20,155),

effective medical therapy is preferable. Although omeprazole would appear to be effective in this situation, the role of this compound in the longer-term management of duodenal ulcer disease remains to be seen.

7.6.5 Safety profile

The powerful healing effects of omeprazole make it a clear candidate drug for use in ulcer therapy. The usefulness of omeprazole is therefore limited solely by potential toxicological problems. In this connection, the safety studies lend further weight to the belief that omeprazole is a safe, well-tolerated compound. In an indirect way, however, the result which has had greatest impact on the clinical use of this drug has been the elevation in serum gastrin. The material presented by Dr Hakansson (Table 7.5 I) and published by his group (101) and a separate group working in Germany (369) suggests that the effect of omeprazole on ECL cells is related to levels of circulating gastrin. No significant difference was present between the effect of omeprazole 30mg and 60mg on serum gastrin. However, when much higher doses of omepraozle are used in rats, with proportionately higher serum gastrin levels, a direct effect of gastrin on ECL cells can be seen.

Both this study and a similar study by Howden et al (172) failed to show any alteration in sex hormone profile during omeprazole therapy. In a volunteer study, however, it has been shown that peak cortisol response to ACTH is reduced during omeprazole therapy (173). Although some drugs possessing the imidazole nucleus have been shown to inhibit the mitochondrial cytochrome P-450 - dependent enzyme 11-hydroxylase (206,302,392), in vitro studies (173) have shown a decrease in deoxycortisol synthesis with omeprazole. It seems unlikely, therefore, that the effect of omeprazole on ACTH-stimulated cortisol is due

entirely to 11-hydroxylase inhibition.

The histological studies were carried out on patients in the fasting, resting state. Apart from an increase in tubular vesicles, no ultrastructural changes were noted. During histamine stimulation in the dog, however, omeprazole causes an inrease in the number of parietal cells with condensed mitochondria, which does not occur with ranitidine (364). One possible interpretation of this is that the increase is a reflection of intracellular i.e. post receptor - blockade.

Liver enzymes showed no deterioration during therapy. No effect of omeprazole was been observed on liver enzymes in other studies either although the effect of omeprazole on liver function, particularly oxidative drug metabolism, has been most closely studied by Langman and co-workers (167). These studies showed a small, dose-related inhibitory effect of omeprazole on drug metabolism but, since this inhibiiton was only observed in the higher dose range, it may not be relevant to clinical use.

Fig 7.6 I **Increase in AUC from Day 1 to Day 7 with 30mg (x) and 60mg (o) daily**

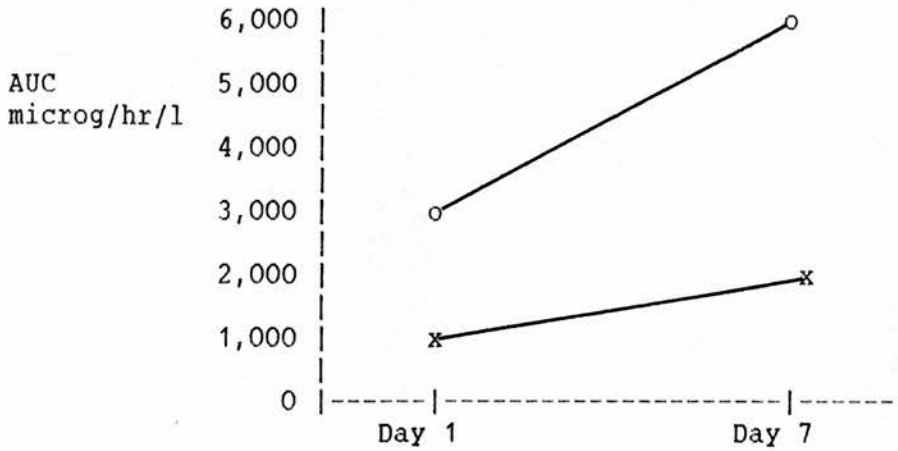
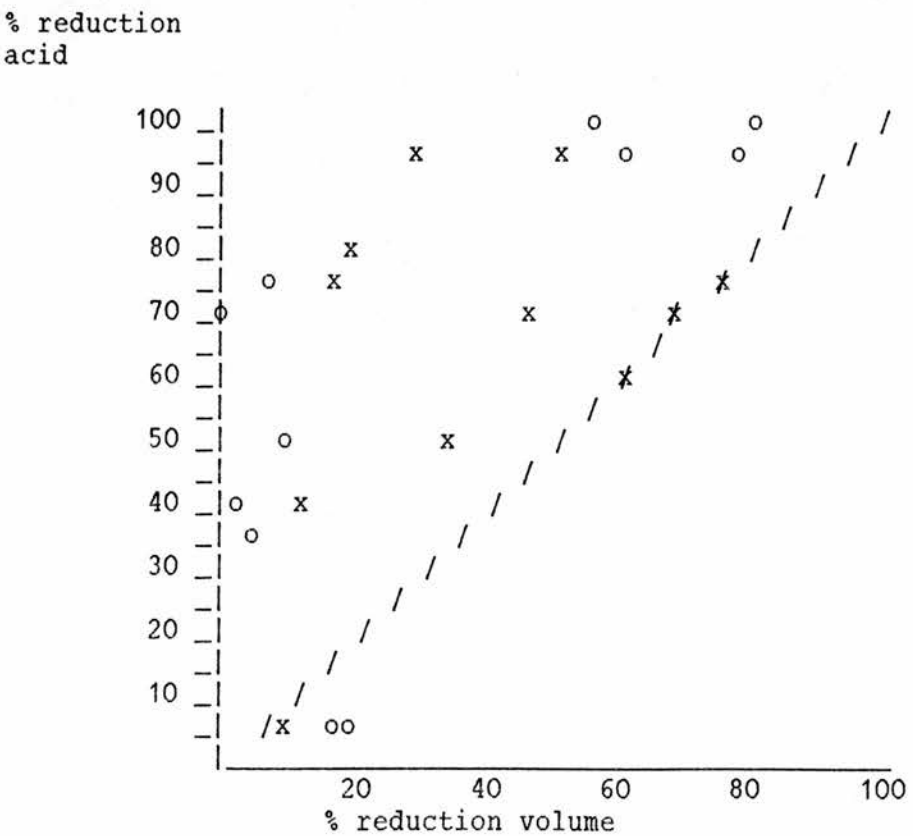


Fig 7.6 II **Plot of % reduction in gastric acid concentration versus % reduction in volume of gastric secretion - subjects and patients after treatment with omeprazole 30mg or 60mg daily for 7 days**



8 DISCUSSION

8.1 Introduction

Patients with ulcers seek medical advice mainly in order to have pain relieved. On the other hand, doctors have two principal therapeutic aims in ulcer disease - to relieve pain and to prevent complications. As both pain and complications occur during ulcer relapse, it follows that a further therapeutic objective must be to prevent relapse. The best means of achieving these aims have not yet been defined and a discussion therefore follows on the relief of symptoms, the healing of ulcers and the prevention of relapse.

The efficacy of ulcer healing drugs and different therapeutic regimens has been primarily assessed in the last decade by clinical trials. As an adjunct to clinical trials, a number of models analysing the impact of therapy on the natural history of ulcer disease have been proposed. In the light of these models, and findings in practice, an approach to ulcer therapy will subsequently be formulated. In addition, the safety of long-term therapy of duodenal ulcer disease will be discussed.

8.2 Pain Relief

The priority for the patient with an active ulcer is the relief of pain. Pain relief during treatment with cimetidine occurs within a few days of starting therapy, and failure to obtain relief should raise the suspicion that the cause of the pain is not a duodenal ulcer (415). Relief of pain occurs equally rapidly with bismuth subcitrate (256), ranitidine (33), omeprazole (308) and enprostil (22).

In Ch 6.4, in a relatively resistant population, I have shown that ranitidine still affords rapid symptomatic relief for the majority of

patients. In those who are truly resistant to H2 receptor antagonists, it is seen in Ch 7.4 that all but two of the patients, both with gastric ulcer, were pain free by day 15 even although the ulcer had not yet healed in a further three patients. Similarly, the studies on maintentance therapy in Ch 6.4 showed that persistent relief of symptoms was achieved despite occasional endoscopically confirmed recurrence, provided that active drug therapy was being used.

8.3 Acute Healing

Since about 70% of ulcers heal in four weeks and 95% in eight weeks, the length of time for acute ulcer healing in clinical trials has been set at four or eight weeks, and a refractory ulcer defined as one which does not heal with standard therapy in two months. A linear relationship has been demonstrated between ulcer healing and time (176). Since it has been shown that incompletely healed ulcers relapse rapidly (290), therapy should be continued until ulcer healing is complete and, in the absence of endoscopic control, ulcer healing treatment should be continued for two months.

Enprostil is not as effective as ranitidine at ulcer healing (22) and trimoprostil only heals 62% of ulcers in a dosage of 0.75mg q.d.s. for four weeks (6). Antacids however, even in low dosage, heal over 80% of duodenal ulcers in four weeks if given four times daily (405), as do both trimipramine (147) and pirenzepine (412). This value is of the same order found during treatment with cimetidine (415), ranitidine (33) and omeprazole (308).

In accordance with general experience, we found that 45 of 68 military patients (66%) healed after four weeks of therapy with

ranitidine (Ch 6.4) and 83% after eight weeks of treatment, despite the relatively aggressive nature of the disease as evidenced by the placebo healing rate of 7.7% at four weeks.

In addition to the ever-increasing range of available drugs, there has also been a gradual shift in the recommended dosage regimens. The initial recommended dosage schedule for cimetidine was 200mg t.i.d. and 400mg nocte (295). As a result of the finding of unsatisfactory compliance with the qds administration of drugs, twice daily regimens were introduced for both cimetidine and ranitidine (207,400). It is not known which aspect of gastric secretion requires inhibition for optimal ulcer therapy, but since one of the most prominent aspects of the pathophysiological abnormalities associated with duodenal ulcer is the inappropriate secretion of acid during the night, it has been suggested that inhibition of nocturnal secretion may satisfactorily heal ulcers. As a result, gastric inhibitory drugs have been administered at bed time and single nocturnal doses have been shown to be equally effective (86,138). A single dose of the powerful anti-secretory agent omeprazole achieves healing rates as good as, or better than, with the H2 receptor antagonists (72) and single nocturnal doses of pirenzepine have also been advocated in an attempt to maximise ulcer healing and minimise side effects (412).

In this connection, Howden et al (176) have analysed the results of 141 published controlled trials and obtained a significant correlation ($r=0.928$) between the degree of gastric inhibition during treatment with H2 receptor antagonists at night only, as reflected by nocturnal intragastric acidity and ulcer healing. By stepwise linear regression, they have determined that the contribution to ulcer healing by the

suppression of nocturnal, as opposed to diurnal, acidity is 86.1%.

The results obtained with the compound ICI 162,846 (Ch 6.3) are therefore particularly interesting. From Howden's studies one would predict that the marked overnight inhibition of gastric acid secretion with this compound should afford a high ulcer healing rate. The return to normal pH values during the day may diminish the potential toxicity of the drug for the gastric mucosa. The gastric acid profile for CM 57755 however is remarkably similar to that obtained with cimetidine and it is likely that this compound does not offer a significant therapeutic advantage.

8.4 Refractory Ulcer

If ulcers do not heal within two months it may be necessary to resort to additional or alternative therapy. Combination therapy, particularly for ulcers which are slow to heal, is an appealing therapeutic concept which is further discussed in Ch 5.2.5. Although greater anti-secretory effects may be achieved (297,304,240), the evidence that any particular combination represents a meaningful advance in treatment is lacking. Omeprazole does represent a therapeutic advantage in this situation, as evidenced by the findings in Ch 7.

8.5 Ulcer Relapse

Unfortunately, after healing virtually all ulcers relapse, about 80% of them within 12 to 24 months of healing. Two different regimens have been proposed for dealing with this relapsing tendency. On the one hand, it has been suggested that patients can be treated whenever a relapse presents symptomatically. The ulcer is then rehealed and

treatment is stopped. This type of regimen has been termed "intermittent therapy" and is based on the assumption that presentation with perforation or haemorrhage is uncommon. Alternatively, an attempt has been made to keep ulcers in remission either surgically or, more recently, by long-term continuous administration of gastric secretory inhibitors ("maintenance therapy") in order to prevent the development of complications.

8.6 Ulcer Models

In 1981 Pounder (305) proposed a model which analysed the contribution of remission and relapse to the "steady state" of clinical ulcer disease occurring during the use of three different therapeutic approaches: administration of placebo only; maintenance treatment with placebo or cimetidine after relapse; and of continuous maintenance treatment with cimetidine, increasing to a healing dosage with the drug after relapse. His findings from observing 100 patients following healing of a duodenal ulcer led him to recommend continuous maintenance therapy. Pounder´s conclusion was in contrast to Bardhan, who also studied approximately 100 patients and recommended that intermittent courses of therapy (treating and healing ulcers only after a symptomatic relapse) were best on the basis of economy and simplicity (18). The difference between the two conclusions depends mainly on the importance which is placed on the prevention of relapse.

Sonnenberg, in 1985, analysed the long term outcome of different strategies in duodenal ulcer disease on the basis of a Markov chain model (363). This hypothetical analysis, along the same lines as the analysis by Pounder made a number of formal assumptions about ulcer relapse, surgical referral and the fate of medically and surgically treated patients. On the basis of the mortality and morbidity of the

current surgical and medical therapy, the analysis led him to recommend maintenance treatment.

In view of the demonstration here in Dundee, and elsewhere, that ulcer recurrence carries with it the risk of complications (haemorrhage and perforation) and death, it seems that maintenance treatment is the therapy of choice for patients with frequent relapses of ulcer disease. Perforation and haemorrhage occur in approximately 15% (10) and 35% (11) respectively of duodenal ulcer patients in the course of their disease and about 2% die (47). The effect of many of the compounds examined in this thesis on the incidence of these complications has not been studied. It is clear, however, from the study of ranitidine in patients whose ulcers had remained healed for one year (Ch 6.4.3) that the incidence of haemorrhage was less in those patients who remained on active therapy. This is also true for maintenance treatment with cimetidine (63) since only four of four hundred patients suffered a complication during four years of maintenance therapy (6).

8.7 Maintenance Regimens

Trimipramine reduces the relapse rate after one year of treatment to around 30% (387) and the relapse rate of 38% with pirenzepine has been tabulated in 5.2.III. Pirenzepine has not found widespread popularity, however, as the therapeutic window between efficacy and dose-related side-effects is relatively narrow.

As demonstrated in Ch 6.4.3, ranitidine given in a dose of 150mg at night will reduce both the number of ulcer relapses. Burland, in 1980, reviewed the results with cimetidine (both in bd and single nocturnal dose) from 22 centres and 696 patients (63). Relapse rate after one year on active therapy was 15% with either regimen, compared

with 48% for placebo. Of the other compounds examined in the preceding chapters, maintenance data are not available for either omeprazole or the prostaglandins.

It is not known whether Fry's concept, that ulcer disease burns itself out after 15 to 20 years (126) is correct or whether, as seems likely from the age-span of the ulcer population, it is a life-long condition. If the ulcer diathesis persists in most patients for life then maintenance therapy must also be given for life in order to minimise the risk of complications.

8.8 Safety of long-term duodenal ulcer therapy

No drug is currently available which will cure the ulcer diatheses -that is, that one course of therapy of which will prevent further relapses. As therapy may have to be continued throughout life the safety of long-term administration clearly becomes paramount.

In addition to problems common to other groups of drugs which are given continuously, those compounds which heal ulcers by reducing gastric secretion - the histamine H2 receptor blockers, omeprazole, pirenzepine and possibly some of the other polcyclic drugs - may give rise to more specific problems. Fears have been expressed (106,102) that prolonged suppression of acid may result in the development of gastric carcinoma. Although these fears find support in the development of gastric tumours in animal studies - carcinoid in rats with omeprazole and at least four different types of neoplastic change in rat gastric mucosa with the H2 receptor antagonists (416) there is no evidence to link those H2 blockers in current use with an increased incidence of carcinoma. Although both cimetidine and ranitidine can be nitrosated in

vitro, neither of these nitrosated compounds are carcinogenic (92,150). In addition to potential carcinogenicity from nitrosated forms of the parent compound, a second route for the formation of nitrosated compounds has been postulated (320). It has been suggested that persistent elevation of intragastric pH permits colonisation of the stomach by bacteria which then reduce dietary nitrate to nitrite. This then complexes with amino groups of food proteins to form nitroso compounds. Although some studies have shown that the concentration of N-nitroso compounds is increased during therapy with cimetidine (320,367), this has not been confirmed (278) and there is no evidence that the actual production of these compounds is increased. The post-marketing surveillance of cimetidine (76) revealed an excess of gastric carcinoma in the cimetidine-treated group, but this was considered due to an excess of pre-existing malignancy in this group due to inappropriate diagnosis.

One possible way of avoiding all such potential problems would be to reserve drugs which act topically, such as sucralfate or even antacid, for long-term use. Both sucralfate and many of the standard antacid preparations contain aluminium however, some of which can be absorbed from the gut (317,136). Some of the potential problems with aluminium toxicity are discused in Ch 3.4

On a less speculative note, it is well recognised that a reduction in gastric acid secretion is a predisposing factor to infection with various enteric pathogenic bacteria (132,133,100) in addition to some parasitic infections such as strongyloidiasis (200), Chagas' disease (288) and schistosomiasis (107). From a metabolic point of view, the possible nutritional consequences of hypochlorhydria include malabsorption of iron (336) and calcium (283). These potential

dangers with cimetidine and ranitidine however, do not seem to be borne out in clinical practice (260,261).

There are a number of other potential side effects of cimetidine. Alteration in renal function (261) and confusion (348) are seen particularly in elderly patients. Loss of libido in males and gynaecomastia have been ascribed to an anti-androgenic effect (413) and a number of drug interactions, such as with warfarin (344), phenytoin (280), propranolol (111) and diazepam (208). These drugs are metabolised in part through hepatic oxidation and this effect has been linked to partial inhibition of the cytochrome P-450 linked mono-oxygenase enzyme system (316). These side effects are not generally observed using maintenance therapy dosage.

Not all side effects may be harmful, since cimetidine has been observed to increase lymhocyte responsiveness in man (294) and raise levels of HDL2-C (one of the sub-fractions of high density lipoprotein which correlates with a diminished incidence of ischaemic heart disease) (411).

8.9 Conclusion

The pharmacological, as opposed to the therapeutic, aim of ulcer therapy must be directed at treating the cause of the disease. That, clearly, is not yet possible but must be what future research is directed toward.

In the interim, the best combination - of efficacy and safety - is, I think, represented by the use of ranitidine 300mg at night to achieve ulcer healing, followed by maintenance therapy of ranitidine 150mg at night in those patients who have established recurrent disease. For

patients with refractory, or resistant, ulcers it is possible that omeprazole or combination therapy with ranitidine and, for example, pirenzepine, would confer benefit.

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